THE

MEDICAL CLINICS

OF NORTH AMERICA

GASTROINTESTINAL AND LIVER DISEASES

VOLUME 52 – NUMBER 6
NOVEMBER, 1968

CORNELL UNIVERSITY
MEDICAL COLLEGE
LIBRARY

Digitized by the Internet Archive
in 2023 with funding from
Kahle/Austin Foundation

https://archive.org/details/lccn_17-28505_52

VETERANS ADMINISTRATION HOSPITALS NUMBER

THE
MEDICAL CLINICS
OF NORTH AMERICA

GASTROINTESTINAL AND LIVER DISEASES

JAMES A. HALSTED, M.D.,
HYMAN ZIMMERMAN, M.D., *Guest Editors*

Volume 52 — Number 6

NOVEMBER, 1968

W. B. SAUNDERS COMPANY – Philadelphia · London · Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, Pa. 19105

12 Dyott Street
London, W.C.1

1835 Yonge Street
Toronto 7, Ontario

© 1968 by W. B. Saunders Company. Copyright under the International Copyright Union. All rights reserved. This publication is protected by copyright. No part of it may be duplicated or reproduced in any manner without written permission of the publisher. Made in the United States of America. Press of W. B. Saunders Company.

The following information is published in accordance with the requirements of the United States Postal Code.

The Medical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08034. Subscription price is $21.00 per year. Second class postage paid at Cherry Hill, New Jersey 08034.

This issue is Volume 52, Number 6.

The editor of this publication is Albert E. Meier, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 17-28505

Contributors to This Issue

RENE A. ALBACETE, M.D., Chief, Gastrointestinal Section, Veterans Administration Hospital; Professor, Department of Internal Medicine, Howard University, Washington, D.C.

KENNETH L. BECKER, M.D., Ph.D., Chief, Section of Metabolism and Genetics, Veterans Administration Hospital; Assistant Professor of Medicine, George Washington University, Washington, D.C.

JAMES D. BOYLE, M.D., Associate Clinical Professor of Medicine, University of California School of Medicine; Chief, Gastroenterology Section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California.

LLOYD L. BRANDBORG, M.D., Assistant Clinical Professor of Medicine, University of California School of Medicine; Chief, Gastroenterology Section, Veterans Administration Hospital, San Francisco, California.

THOMAS C. CHALMERS, M.D., Assistant Chief Medical Director for Research and Education, Veterans Administration, Washington, D.C.; formerly Professor of Medicine, Tufts University School of Medicine, and Chief of Medical Services, Lemuel Shattuck Hospital, Boston, Massachusetts.

HAROLD O. CONN, M.D., Chief, Hepatic Research Laboratory, Veterans Administration Hospital, West Haven; Associate Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut.

H. MARTIN ENGLE, M.D., Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, Washington, D.C.

JAMES D. FINKELSTEIN, M.D., Assistant Professor of Medicine, George Washington University; Chief, Hepatology Section and Biochemistry Research Laboratory, Veterans Administration Hospital, Washington, D.C.

HOWARD GOLDSTEIN, M.D., Assistant Professor of Medicine, University of California School of Medicine; Associate Chief, Gastroenterology Section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California.

MORTON I. GROSSMAN, M.D., Ph.D., Professor of Medicine and Physiology, University of California School of Medicine; Senior Medical Investigator, Veterans Administration Center, Los Angeles, California.

CHARLES A. HALL, M.D., Associate Chief of Staff, Veterans Administration Hospital; Professor of Medicine, Albany Medical College, Albany, New York.

JAMES A. HALSTED, M.D., Professor of International Health, Department of Epidemiology and Environmental Health, George Washington University School of Medicine; Associate Chief of Staff for Research and Education, Veterans Administration Hospital, Washington, D.C.

DONALD H. HANSCOM, M.D., Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago; Research Physician, Veterans Administration Hospital, Hines, Illinois.

PAUL H. JORDAN, JR., M.D., Chief of Surgery, Veterans Administration Hospital; Professor of Surgery, Baylor University School of Medicine, Houston, Texas.

CARROLL M. LEEVY, M.D., Professor of Medicine and Director of the Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine and Dentistry, Jersey City; Chief of Medicine, Veterans Administration Hospital, East Orange, New Jersey.

RODRIGO MENENDEZ-CORRADA, M.D., Assistant Clinical Professor of Medicine, University of Puerto Rico Medical School; Chief, Hematology Section, and Acting Associate Chief of Staff for Research, Veterans Administration Hospital, San Juan, Puerto Rico.

W. W. PETERNEL, M.D., Assistant Professor of Medicine, University of Kentucky; Assistant Physician, University of Kentucky Medical Center, Lexington, Kentucky; formerly Chief, Gastroenterology, Veterans Administration Hospital, and Assistant Professor of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

ELIHU M. SCHIMMEL, M.D., Assistant Professor of Medicine, Boston University School of Medicine; Chief, Gastroenterology Section, Veterans Administration Hospital, Boston, Massachusetts.

JOHN A. SIMPSON, M.D., Clinical Instructor of Medicine, Yale University School of Medicine, New Haven, Connecticut.

MARVIN H. SLEISENGER, M.D., Chief, Medical Service, Veterans Administration Hospital; Professor and Vice Chairman, Department of Medicine, University of California School of Medicine, San Francisco, California.

JULIUS WENGER, M.D., Chief, Gastroenterology, and Assistant Chief, Medical Service, Veterans Administration Hospital; Associate Professor of Medicine (Gastroenterology), Emory University School of Medicine, Atlanta, Georgia.

LESLIE ZIEVE, M.D., Professor of Medicine, University of Minnesota; Associate Chief of Staff, Minneapolis Veterans Hospital, Minneapolis, Minnesota.

HYMAN J. ZIMMERMAN, M.D., Professor of Medicine, Boston University School of Medicine; Chief of Medical Service, Veterans Administration Hospital, Boston, Massachusetts.

Table of Contents

SYMPOSIUM ON GASTROINTESTINAL AND LIVER DISEASE

INTRODUCTION 1265
H. Martin Engle, M.D.

FOREWORD 1267
James A. Halsted, M.D.; Hyman J. Zimmerman, M.D.,
GUEST EDITORS

PART I

SOME IMPLICATIONS OF CURRENT RESEARCH IN GASTROENTEROLOGY 1269
Marvin H. Sleisenger, M.D.

GENETIC ASPECTS OF GASTROINTESTINAL DISEASE 1273
Kenneth L. Becker, M.D., Ph.D.

AUTOIMMUNE MECHANISMS AND THE GASTROINTESTINAL TRACT ... 1285
Charles A. Hall, M.D.

GASTROINTESTINAL HORMONES 1297
Morton I. Grossman, M.D., Ph.D.

CLINICAL ASPECTS OF GASTRIC SECRETION AND GASTRIC ANALYSIS 1305
Paul H. Jordan, Jr., M.D.

CYTOLOGICAL EXAMINATION IN GASTROINTESTINAL TRACT DISEASE 1315
Lloyd L. Brandborg, M.D.; Julius Wenger, M.D.

RECENT SYMPOSIA

January, 1968 – *from Chicago*
PAIN AND ITS CLINICAL MANAGEMENT

March, 1968 – *from St. Louis*
ENDOCRINE DISORDERS

May, 1968 – *Nationwide*
RHEUMATOID ARTHRITIS

July, 1968 – *Mayo Clinic*
NEUROLOGIC DISORDERS

September, 1968 – *Nationwide*
RECENT ADVANCES IN CARDIOVASCULAR DISEASE

FORTHCOMING SYMPOSIA

January, 1969 – *from Chicago*
ADVANCES IN LABORATORY DIAGNOSIS
PETER J. TALSO, M.D., *Guest Editor*

March, 1969 – *from the Lahey Clinic*
DIFFICULT PROBLEMS IN DRUG THERAPY
HENRY E. ZELLMAN, M.D., *Guest Editor*

May, 1969 – *from New York University*
REHABILITATION
EDWARD W. LOWMAN, M.D., *Guest Editor*

July, 1969 – *Nationwide*
GENETICS IN CLINICAL MEDICINE
PHILIP L. TOWNES, M.D., *Guest Editor*

September, 1969
1. COMMON EYE DISORDERS AND INJURIES
ARTHUR H. KEENEY, M.D., *Guest Editor*
2. PROBLEMS IN REPRODUCTION AND SEXUAL ADJUSTMENT
F. JACKSON STODDARD, M.D., *Guest Editor*

SYMPOSIUM ON GASTROINTESTINAL AND LIVER DISEASE

Introduction

H. MARTIN ENGLE, M.D.

A significant percentage of all illness is related to the gastrointestinal tract and these diseases constitute a major cause of hospitalization and disability. Data available for the Veterans Administration indicate an importance comparable to that for the nation as a whole.

In recent years about 110,000 patients per year have been admitted to Veterans Administration Hospitals for treatment of gastrointestinal complaints. This represents 16 per cent of all admissions. In addition there are about 130,000 veterans receiving compensation for service-connected disease in this category. The annual cost to the taxpayer for these combined responsibilities is a formidable total of close to $200 million. More important, the magnitude of the problem presents a challenge from the standpoint of research and education.

Many of the recent advances in gastroenterology and liver disease have been made by physicians of the Veterans Administration. It is gratifying to note that the list of contributors to this volume includes the immediate past President and the President of the American Gastroenterological Association, the Editor of Gastroenterology, and a number of Professors of Medicine and Surgery in Medical Schools, all employees of the Veterans Administration who direct major Services, or Divisions of Gastroenterology in VA Hospitals.

About 10 per cent of our research budget is currently expended for studies of the tubular gastrointestinal tract, liver, and pancreas. The breadth of interest and the varied research disciplines utilized by our investigators is evident in a review of this volume. As would be expected in a hospital-based system most of the research effort is clinically oriented, but basic studies have secured necessary support and will continue to merit appropriate attention.

We are initiating a training program in gastroenterology that will have as objectives the training of physicians for careers in patient care, in teaching, in research, or combinations of these.

In research and education, as well as in patient care resources, more attention should be paid to the specialty of gastroenterology. Our efforts in the Veterans Administration are directed not only to our own problems but to the needs of all mankind.

H. MARTIN ENGLE, M.D.

Chief Medical Director
Department of Medicine and Surgery
Veterans Administration

Foreword

J. A. HALSTED, M.D.

H. J. ZIMMERMAN, M.D.

Our efforts in organizing this volume have been directed toward presenting basic science aspects of gastroenterology and liver disease and their clinical implications. We have not attempted to deal with the day-to-day clinical problems, because these can be found in recent textbooks. Rather, we have focused on some major aspects of gastroenterology in which recent knowledge has provided the more fundamental understanding of disease that is necessary for rational therapy. Accordingly, discussion of electron microscopy, which is still a research tool rather than a practical aid to diagnosis and therapy, has been omitted. At the same time, new data leading to new concepts essential for modern practice have accumulated in the areas of autoimmunity, intestinal absorptive processes, genetics, physiology, and endocrinology. Articles bearing on each of these fields will be found in this issue.

Gastrointestinal disease is one of the leading causes of hospitalization and of inability to work because of illness. Nevertheless, financial support for research in gastrointestinal disease, the number of specialists in the field, and the number of full-time faculty members specializing in gastrointestinal disease are disproportionately low. However, the changing character of gastroenterology bids fair to assure that this situation will eventually be altered as greater numbers of young investigators become attracted to the field in proportion to its importance. Funds adequate to support basic research in the field will become available as more well-trained and imaginative minds come on the scene. Until recently, gastroenterology was largely descriptive and empiric. Contributions of the biochemist, the physiologist, the cell biologist, and the immunologist are now beginning to bring more precise and more basic understanding. With this better understanding of disease processes, more rational therapy is becoming possible in diseases of the digestive system.

Because it is self-evident that gastrointestinal disorders may lead to malnutrition – "conditioned malnutrition" if you will – a short article has been devoted to summarizing some of the relationships between these two areas of medicine.

There is always some controversy and disagreement as to whether diseases of the liver "belong" to gastroenterology. Without entering this controversy, we have chosen to divide the volume into two parts. Part I is devoted to disorders of the tubular gastrointestinal tract and Part II is concerned with the liver and pancreas – the solid organs. Space limitation dictated that we omit the gallbladder entirely, as well as detailed considerations of newer aspects of endoscopy such as the fiberscope.

The opportunity to edit an issue of *The Medical Clinics* devoted to gastroenterology and liver disease has been challenging and satisfying, because we see in this field of medicine the likelihood of continuously more rapid progress in medical science. An ultimate solution to many baffling problems which have exacted such a heavy toll in disability and life now appears to be within grasp.

JAMES A. HALSTED, M.D.
HYMAN J. ZIMMERMAN, M.D.
Guest Editors

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422 (Dr. Halsted)

Veterans Administration Hospital
150 South Huntington Avenue
Boston, Massachusetts 02130 (Dr. Zimmerman)

Some Implications of Current Research in Gastroenterology

MARVIN H. SLEISENGER, M.D.*

Laboratory research in gastroenterology, applicable to diagnosis and treatment of disease, has advanced remarkably in the past decade. For example, significant studies have taken place in the areas of motility, gastrointestinal hormones, absorption and malabsorption, and the hepatocellular effect of drugs and toxins. The sections that follow will deal with specific investigative and clinical aspects of these important gastrointestinal disease entities.

Motility

Satisfactory techniques for measuring intraluminal pressure have made possible clearer classification of a number of diseases and disorders of the esophagus. Abnormalities of peristalsis and function of the gastroesophageal sphincter are revealed by open-tipped, constantly perfused catheters, or by small water-filled balloons, attached to appropriate pressure sensors and recorders. Differential diagnosis of achalasia, carcinoma, diffuse spasm, and scleroderma is greatly facilitated by these methods. Indeed, manometric response of the esophagus in achalasia to methacholine (Mecholyl) is considered pathognomonic for the disease.

Research in endoscopy, specifically the development of fiberoptic instruments, is exposing the gastric mucosa clearly for both the eye and the camera. Passage is easier and safer, encouraging wider usage of this technique, which is facilitating accurate diagnosis of diseases of the esophagus and stomach.

Gastrointestinal Hormones

Edkin in 1905 reported an increase in gastric secretion following the injection of an extract of the mucosa of the pyloric gland area of the stomach; he named this extract gastrin. Sixty years later Gregory and others conclusively proved the existence of the hormone by isolating and

---

*Chief, Medical Service, San Francisco Veterans Administration Hospital; Professor and Vice-Chairman, Department of Medicine, University of California, San Francisco Medical Center, San Francisco, California; Editor, Gastroenterology

purifying gastrin, determining its structure, and synthesizing the compound.

Gastrin is a small polypeptide consisting of 17 amino acids with a molecular weight of 2000. The C-terminal tetrapeptide amide group (Try-Met-Asp-Phe-NH_2) is the active portion and reproduces all of the physiological properties of the total molecule.

Physiological studies with gastrin have shown its effects to include (1) powerful stimulation of gastric acid secretion; (2) weak stimulation of pepsin secretion; (3) weak stimulation of pancreatic flow and bicarbonate output; (4) strong stimulation of pancreatic enzyme output; and (5) weak stimulation of hepatic biliary flow and bicarbonate output. The effect of gastrin on gastric motility is less clear, but recent work suggests stimulation of antral motility with doses of gastrin that could be expected to approximate levels found during endogenous release.

The pentapeptide of gastrin has been used extensively in countries outside the United States as a stimulant for acid secretion during gastric analyses in man. It appears to be a safe and satisfactory stimulant, producing acid secretory responses similar to those found during maximal histamine stimulation. Dose schedules producing maximal secretion during gastrin stimulation have been established, and it appears that significant reactions to the tetrapeptide are unusual.

Antibodies to the whole gastrin molecule and fractions thereof have recently been produced. Several biological assays and radioimmunoassays are currently being developed and blood levels of gastrin are being measured. This exciting work obviously may provide the means for relating gastrin to peptic ulcer disease. However, since the C-terminal tetrapeptide amide of gastrin and cholecystokinin-pancreozymin cross react to antibodies developed against the gastrin tetrapeptide, the search is one for antibodies specific for the distinctive portions of both gastrin and cholecystokinin-pancreozymin.

Measurement of gastric secretory response to stimulation with histamine, betazole (Histalog), gastrin, or the pentapeptide of gastrin has been more or less standardized during the past few years, permitting accurate clinical evaluation of gastroduodenal diseases, particularly peptic ulcer. It is now clear that subcutaneous injections of all these stimulants correlate with maximal responses obtained intravenously; also, that equally accurate estimates of secretion can be obtained from the subcutaneous or intravenous use of any stimulant. The choice of one mode of administration in preference to another is largely one of expediency and design.

Elaboration of excessive amounts of gastrin by non-β-islet cell tumors of the pancreas results in tremendous hypersecretion of acid gastric juice and in peptic ulcer disease. Such tumors may also cause severe diarrhea and hypokalemia without an increase in gastric secretion (indeed, there may be hyposecretion). The evidence suggests that a hormonal substance affects the small bowel, causing "hypersecretion" of intestinal fluid; no absorption defect for water or potassium ion has been demonstrated.

Another example of the elucidation of the hormonal basis for serious clinical symptoms is the carcinoid syndrome. Gastrointestinal symptoms are caused by the release of 5-hydroxytryptamine (serotonin, 5-HT) from metastatic carcinoid tumor in the liver. In vitro and in vivo studies show that 5-HT has a potent effect on gut motility. Current investigations of this effect indicate that 5-HT may have a physiological role in gut function, perhaps by facilitating autonomic control of peristalsis.

Absorption and Malabsorption

Diagnosis of the small bowel diseases which cause malabsorption continues to be facilitated by peroral biopsy of the jejunal and ileal mucosa. Thus, the list of pathological conditions associated with absorptive defects continues to grow. Small bowel biopsy likewise has contributed enormously to our understanding of the normal absorption mechanism at the cellular level, particularly when electron microscopy and autoradiography are employed.

Mucosal biopsy also facilitates study of cell replication, which sheds light on factors regulating cell turnover. These investigations provide a possible avenue of approach to the transformation of the normal growth pattern of gut epithelium to the abnormal one of malignant disease.

Technological advances in bile salt analyses have led to studies designed to reveal their role in biological processes. The bile salts are synthesized from cholesterol in the liver and their taurine and glycine conjugates excreted in bile. About 24 gm. of bile salt enter the duodenum per day and about 98 per cent is reabsorbed, mostly from the ileum. The extraction of the bile salts from the blood derived from the portal vein and active secretion into bile by the liver cell is a major cause for normal bile flow. Abnormalities of bile salt metabolism, such as excessive production of sodium lithocholate, may cause a syndrome of cholestasis.

In the intestines the bile salts have two major roles. The rate of cholesterol synthesis by small intestinal mucosa is regulated by the bile salts. Diversion of the bile salts by biliary drainage or by binding to ion exchange resins leads to a large increase in intestinal cholesterol synthesis. In the jejunum the micellar structure of the bile salts keeps the fatty acids and 2-monoglycerides in soluble form, permitting their absorption. Reduction in the number of micelles causes a decrease in absorption of the products of lipolysis, leading to steatorrhea. Also, alteration of the bile salt micelle in gallbladder bile may be the key to precipitation of cholesterol, initiating cholelithiasis.

The microbiology of the upper intestine is now better understood. Normally, coliform and anaerobic organisms achieve a total concentration of 10^3 per ml. or less; however, special techniques must be used for culture of the latter group. When bacteria exceed this density, deconjugation of bile salts may ensue. The practical application of this information has led to the clear emergence clinically of the "blind loop" syndrome and to effective therapy with surgery, if appropriate, or with antimicrobial drugs.

The concept of the micelle has explained a great deal about the mechanism of breakdown and solubilization of neutral fat. Measurement of this complex physicochemical arrangement of monoglycerides, fatty acids, and bile salts now permits tentative conclusions to be made about the pathogenesis of steatorrhea in a number of diseases of malabsorption. Such studies may be carried out after ingestion of a known amount of triglyceride. Analysis of jejunal aspirates for conjugated bile salt concentration and for per cent lipid in micellar phase, along with quantitative culture of the bacterial population, will roughly indicate the relative importance of interruption of the enterohepatic circulation of bile salts and of excessive deconjugation. Acid pH or pancreatic insufficiency will inhibit the action of lipase and, thus, the hydrolysis of triglyceride. Further knowledge of bile salt metabolism should thus lead to more effective means for the prevention of cholestasis, cholelithiasis, hypercholesterolemia, and steatorrhea.

Conclusion

The preceding discussion has highlighted progress in four areas of research endeavor in gastroenterology. Consideration of the important advances in understanding of liver disease, especially the effects of hepatotoxins, has not been undertaken here, since these are discussed in Part II. Although clinical application of laboratory evidence necessarily is slow, we may confidently expect it to increase. Continued research along the lines discussed here may well lead to sufficient understanding of the etiology and pathogenesis of a host of diseases, ranging from hepatobiliary disease and the malabsorption syndrome to atherosclerosis and gastrointestinal cancer. The clinical emphasis may then shift from diagnosis and therapy to prevention. In the years to come we may confidently expect continuing progress.

San Francisco Medical Center
Third & Parnassus Avenues
San Francisco, California 94122

Genetic Aspects of Gastrointestinal Disease

KENNETH L. BECKER, M.D., Ph.D*

As a result of the recent growth of interest in human genetic disease, many heritable conditions have been revealed in which the gastrointestinal tract is affected. Similarly, clinical and laboratory studies of the various gastrointestinal diseases have clarified or revealed heretofore vague or unsuspected genetic influences.

The gene has a broad mission: it must perpetuate itself within the body, and be propagated beyond the confines of that body to insure the continuance of the species. In addition, the gene has the ultimate and primary responsibility for inducing somatic structure and organization during development, and for maintaining biochemical function in adulthood. It is the sequence of bases in the DNA molecule which determines the identity and nature of a gene. The principal action of many genes is to specify the amino acid content and sequence of polypeptides. Indeed, it appears that the motive force in protoplasm is the translation of DNA sequences into specific polypeptide sequences, which may be enzymes or structural proteins. Hence, via the intermediary of protein synthesis, it is the genes which ultimately determine ontogeny and lead to the development in the individual of the physiological and morphological aspects of the phenotype.

Genetically determined gastrointestinal disease may be manifested by altered *function* or altered *structure*. For discussion, the term "altered function" will be used to denote abnormal physiological or pathological action. This dysfunction may or may not be dependent upon aberrations in enzymatic biochemical processes. The term "altered structure" will be used to denote genetically determined morphological anomalies in which there is no readily apparent enzyme abnormality.

For the purposes of this discussion, the genetic aspects of gastrointestinal disease have been subdivided into five arbitrary categories:

1. Single-gene gastrointestinal disease of altered structure
2. Single-gene gastrointestinal disease of altered function
3. Primary gastrointestinal disease with extragastrointestinal symptomatology

---

*Chief, Section of Metabolism and Genetics, Veterans Administration Hospital; Assistant Professor of Medicine, George Washington University, Washington, D.C.

4. Nongastrointestinal disease with occasional associated gastrointestinal symptomatology.
5. Polygenic influences on gastrointestinal disease

SINGLE-GENE GASTROINTESTINAL DISEASE OF ALTERED STRUCTURE

The phenogenesis of structural traits is particularly complex because it involves not only the synthesis of protein, but also cellular organization and differentiation. Clinically, those diseases of altered structure in which the heritable influences appear to be most apparent are single-gene diseases. An excellent example of single-gene gastrointestinal disease of altered structure is the Peutz-Jeghers syndrome. In 1921 Peutz[54] described a family with polypoid lesions of the bowel and skin hyperpigmentation. After several other reports of similar cases had appeared in the literature, Jeghers and co-workers[35] reported 10 additional patients and described the clinical and genetic aspects of the syndrome. In addition to polyposis, these patients manifest melanin pigmentation of the lips, the oral mucosa, and occasionally the fingers. The polyps involve primarily the small intestine, but may occur elsewhere in the gastrointestinal tract; they are rarely, if ever, premalignant. This syndrome is an excellent example of *pleiotropism*—that is, multiple effects of a single gene.

The pattern of transmission within the pedigree of the Peutz-Jeghers syndrome is typical of mendelian dominant inheritance: transmission of the trait is vertical from one generation to the next. Theoretically, 50 per cent of the children of one unaffected parent and one heterozygously affected parent will have the trait; the normal relatives of an affected person will have normal children.[8] In actuality, the inheritance of Peutz-Jeghers syndrome is less clear-cut because of variability in penetrance and expressivity, and perhaps because of mutations.

Familial polyposis of the colon,[21] another example of a single-gene gastrointestinal polyposis, is somewhat more common than the Peutz-Jeghers syndrome. This disease, which also exhibits dominant transmission, may vary in severity from several isolated adenomas to involvement of the entire colon and rectum with multiple polyps. In contrast to the Peutz-Jeghers syndrome, there is no associated mucocutaneous pigmentation. The polypoid lesions frequently give rise to colonic carcinoma which may occur at an early age, is often multicentric, and grows rapidly. A distinct variety of intestinal polyposis, termed Gardner's syndrome,[24] also transmitted dominantly, is associated with epidermoid cysts, fibromas of the soft tissues, and osteomas of the skull. The polyps may occasionally involve the small intestine and are premalignant.

Genetic disease of altered gastrointestinal structure can be clinically evident at birth. Thus, anorectal anomalies (imperforate anus or rectal fistula) with apparently dominant transmission have been noted in several familes.[37, 63] Weinstein[73] reported three families with imperforate anus in which X-linked recessive inheritance seemed likely, while the cases of Van Gelder and Kloepfer[65] suggested autosomal recessive inheritance. The lack of uniformity in the transmission of these defects suggests a heterogeneity of genetic causes (nonallelism). It should be noted, however, that most cases of imperforate anus appear to be isolated occurrences, and only rarely are there any heritable influences discernible.

Other examples of single-gene structural diseases include familial extrahepatic biliary atresia of seemingly recessive inheritance,[10] a pedigree of apparently autosomal dominant bilateral inguinal herniae which involved males of four generations,[72] and situs inversus viscerum of suspected autosomal recessive transmission.[17]

SINGLE-GENE GASTROINTESTINAL DISEASE OF ALTERED FUNCTION

As the elegance of biochemical, analytical, and diagnostic techniques increases, so does the list of known genetically induced diseases of altered gastrointestinal function. Occasionally, it appears that a biochemical or enzymatic defect causes the dysfunction, although more frequently no specific metabolic error has been elucidated. Since many of these illnesses have been described only recently, knowledge concerning the mode of inheritance is often rudimentary. Thus, the description of a disease in two or more members of several sibships without apparent parental morbidity suggests recessive transmission, as does the description of one or more involved children born of uninvolved parents who are consanguineous. For example, recessivity has been postulated by Sheldon[60] in his report of two unrelated sibships with congenital absence of pancreatic lipase. The parents were normal. The illness was characterized by oily, floating, bulky stools, with normal somatic growth and without associated abdominal distention, anemia, or abnormal sweat electrolyte concentrations. Analysis of the duodenal aspirate demonstrated deficiency or absence of pancreatic lipase. The children responded to treatment with pancreatic extract. On the other hand, involvement of three successive generations with a bizarre myopathy characterized by the insidious onset in late life of slowly progressive dysphagia and symmetrical ptosis of the eyelids (oculopharyngeal muscular dystrophy) led Victor and co-workers[66] to conclude that this disease was transmitted dominantly.

Gross and co-workers[28, 29] have demonstrated that even a variety of pancreatitis may be determined by a single-gene defect. These patients are characterized by a clinical history similar to that of chronic relapsing pancreatitis except for early age of onset, equal sex incidence, stones in the larger pancreatic ducts, and infrequency of accompanying alcoholism or gallstones. Some of these patients excrete abnormal amounts of cystine and lysine in the urine. The disease appears to be transmitted as a dominant trait.

The highly inbred old order Amish have been a fertile source for genetic studies. Byler's disease, or fatal familial intrahepatic cholestasis,[16] has been found in these isolates. Children with this disease manifest early onset of loose foul-smelling stools, recurrent jaundice, hepatosplenomegaly, dwarfism, elevated serum alkaline phosphatase, and normal to low serum cholesterol. Transmission appears to follow an autosomal recessive pattern. Another form of genetic nonhemolytic jaundice is the Crigler-Najjar syndrome.[15, 18] This severe, persistent neonatal disease is characterized by a defect of glucuronic acid conjugation of bilirubin (glucuronyl transferase deficiency).[64] The sibship aggregation found in this disease strongly suggests that these patients are homozygous for a mutant gene, the illness therefore being transmitted recessively.

Another inborn error of bilirubin metabolism is the Dubin-Johnson syndrome, a genetic defect of bilirubin excretion transmitted as an autosomal dominant with much variability of expression. Clinically, there is hyperbilirubinemia of the conjugated type, increased retention of bromsulphalein dye, frequent nonvisualization of the gallbladder, and abnormal pigmentation of the liver parenchyma.[13]

There appear to be several single-gene defects of intestinal absorption. Among these, the heritable deficiencies of sugar-splitting enzymes are arousing considerable attention. Congenital juvenile sucrase and isomaltase deficiency is characterized by diarrhea induced by sucrose or isomaltose ingestion, which is ameliorated by dietary exclusion of these sugars.[39] The mode of transmission of this disease is uncertain. An analogous disease, primary monosaccharide malabsorption, apparently is due to a defect in the active transport of glucose galactose across the mucous membrane of the intestine. Fructose absorption is normal, as is disaccharidase activity. Histologically, the intestinal mucosa appears normal. This disease, which manifests as severe diarrhea in infants after commencement of breast feeding, may be transmitted recessively.[1]

Another recently described genetic disease of intestinal malabsorption is familial protein intolerance with deficient transport of basic amino acids.[38] The children manifest an aversion to protein-rich foods, episodes of diarrhea and vomiting, dwarfism, hyper-ammonemia, deficient rise in plasma urea levels following protein intake, aminoaciduria, and hepatomegaly which may eventuate in diffuse cirrhosis. The mode of inheritance appears to be recessive.

Evidence that the entire spectrum of manifestations and physical findings known as hemochromatosis is a genetic disease of abnormal intestinal absorption of iron is as yet insufficient and controversial. The criteria for diagnosis are disputed and the etiologic relationship to alcoholism is unresolved. However, Powell's [56] study of iron storage in relatives of patients with hemochromatosis and in relatives of patients with alcoholic cirrhosis and hemosiderosis supported the belief that the two diseases are distinct entities, and that idiopathic hemochromatosis is genetically determined. A clinical and pedigree study by Debré and coworkers[19] led to the conclusion that the idiopathic hemochromatosis patient may be heterozygous, and that some cases of juvenile hemochromatosis may be homozygous. Studies by other investigators have also emphasized the heritable aspects of this disease, but the mechanism of transmission is, as yet, uncertain.[53, 74, 75]

PRIMARY GASTROINTESTINAL DISEASE WITH EXTRAGASTROINTESTINAL SYMPTOMATOLOGY

There are several genetic diseases in which some or all of the causative factors may reside in the gastrointestinal tract, yet severe extragastrointestinal symptoms may occur, or may even dominate the clinical picture. One example of such a disease is congenital beta-lipoprotein deficiency. These patients have steatorrhea, diffuse disease of the nervous system, occasional retinitis pigmentosa, and abnormal spiny-appearing erythrocytes (acanthocytes). Beta or low-density lipoproteins are absent or diminished, and it appears that these patients have a recessively transmitted inability to form the beta-lipoprotein molecule. The decrease in blood lipids appears to be due to the deficient lipoprotein transport, and the neurologic manifestations (neuropathy, ataxia) conceivably may be related to this primary defect.[34]

Pernicious anemia is another disease in which some of the manifestations are extragastrointestinal, but in which the pathophysiologic abnormality apparently resides in the gastrointestinal tract. This abnormality is defective synthesis by gastric mucosa of the mucoprotein intrinsic factor necessary for intestinal transport of vitamin B_{12}.[76] According to some investigators, adult pernicious anemia appears to follow an autosomal dominant inheritance pattern.[18] Others have postulated that some forms of familial juvenile pernicious anemia might be due to homozygosity for a gene responsible for deficient secretion of intrinsic factor.[69]

NONGASTROINTESTINAL DISEASE WITH OCCASIONAL ASSOCIATED GASTROINTESTINAL SYMPTOMATOLOGY

Although principally entodermal in origin, the gastrointestinal system does not develop or function independently of other body systems. Thus, there are various genetic diseases which are not primarily diseases of the gastrointestinal tract but which occasionally result in gastrointestinal pathology or symptomatology. For example, Marfan's syndrome, a diffuse disease of connective tissue, has been associated with diaphragmatic hernia and with diverticulosis and diverticulitis of the colon.[49, 51] In such cases, it is not difficult to imagine that the same connective tissue defect which results in lax joints and dislocated lenses may also involve the gastrointestinal tract. Similarly, the genetic disease myotonia dystrophica (muscular wasting, lenticular opacities, frontal baldness, testicular atrophy) may involve the pharynx and esophagus.[55]

Nongastrointestinal disease may cause abdominal pain. Acute intermittent porphyria is an inherited disease which is primarily due to abnormal pyrrole pigment metabolism, but which may cause severe episodes of abdominal pain simulating surgical emergencies.[70] (Of course, since the liver may be the source of the porphyrin dyscrasia, one might justifiably prefer to call this a gastrointestinal disease.) Similarly, severe attacks of abdominal pain are found in association with diffuse angiokeratoma of Fabry. The pedigree data are consistent with X-linked recessive transmission of this disease – for example, predominance of involved males, no or minimal involvement by the carrier female, and no father-to-son transmission.[36]

One of the earliest described human genetic diseases is hereditary hemorrhagic telangiectasia, a disease of dominant transmission characterized by multiple, sharply circumscribed, flat telangiectatic lesions of the face, lips, tongue, and mucosal surfaces of the respiratory, urinary, and gastrointestinal tracts.[32] When the latter is involved, the patient is subject to hematemesis or melena. Gastrointestinal involvement in the dominant disease, neurofibromatosis, can also result in gastrointestinal bleeding,[23] as can that genetically determined disease of elastic tissue, pseudoxanthoma elasticum.[77] Blood in the stools is also seen in the X-linked Aldrich syndrome (eczema, thrombocytopenia, increased liability to infections).[3]

Severe intractable peptic ulcer is recognized as being a gastrointestinal complication or concomitant feature of the dominantly transmitted syndrome of multiple endocrine adenomatosis (varying combinations of adenomas of the pituitary, parathyroids, pancreas, thyroid, and adrenal cortex.)[7] The extent of the relationship between this entity and the Zollinger-Ellison syndrome is, as yet, unclear.

Cirrhosis of the liver appears to be an occasional or frequent manifestation of several genetically determined diseases. The cirrhosis of the liver which is found in the recessively transmitted Wilson's disease (hepatolenticular degeneration) is common enough to be considered part of this syndrome, which is apparently due to an inborn error of copper metabolism.[5] Galactosemia is an inborn error of metabolism in which there is a recessively inherited deficiency of galactose-1-phosphate uridyl transferase. It is associated with hepatic cirrhosis, as well as cataracts, feeding disturbances, and mental retardation.[68] The biliary cirrhosis of the recessively transmitted disease mucoviscidosis (cystic fibrosis of the pancreas) is frequently only part of the total picture of pancreatic exocrine deficiency, sweat gland dysfunction, and chronic bronchopulmonary infection.[44]

Progressive poliodystrophy with cirrhosis of the liver is a newly discovered disease which appears to be familial. It is characterized by convulsions, mental and growth retardation, atrophy of the cerebral gray matter, jaundice, and hepatic cirrhosis.[71] Still another heritable disorder which may result in cirrhosis of the liver is tyrosinosis. This recessively transmitted disease appears to be due to a congenital lack of p-hydroxyphenyl-pyruvate oxidase, leading to abnormal tyrosine metabolism with elevated serum tyrosine levels and increased excretion of this amino acid and its metabolites in the urine. This usually fatal disease of infants and children is characterized by vomiting and diarrhea, failure to thrive, abdominal distention, hepatic cirrhosis with hepatosplenomegaly, and renal tubular defects with vitamin D–resistant rickets.[31]

POLYGENIC INFLUENCES ON GASTROINTESTINAL DISEASE

More commonly than not, gastrointestinal disease is determined or modified by multiple genetic factors which, as is the case with single-gene diseases, must interact with a myriad of environmental influences. Such a composite effect which is dependent on the interaction of several genes is termed *polygenic inheritance*. Because of the complexity of genic interactions, it is impossible to analyze this variety of inheritance by the classic pedigree methods.

A good example of polygenic influences acting upon gastrointestinal disease may be found in carcinoma of the stomach. There is no doubt that genetic factors are of importance in connection with some forms of cancer, the literature being replete with data suggesting that susceptibility to cancer may be inherited.[15] Of course, susceptibility to disease does not necessarily mean morbidity. Whether cancer is due to latent viruses, carcinogenic substances, or somatic cell mutations, it is clear that in certain circumstances genetic factors can alter its incidence, progression, and manifestations. Perhaps because of its frequency, gastric cancer has been the subject of considerable genetic investigation. These various studies, though often not conclusive, have been particularly interesting.

It is known that the incidence of carcinoma of the stomach varies greatly in different regions of the world. Although the incidence appears to be decreasing in the United States, it is extremely high in Japan, where stomach cancer causes roughly 50 per cent of all deaths from malignant diseases in males. There is a lower death rate from stomach cancer among Japanese immigrants in California than there is in Japan.[12] Thus, since migrants from high-risk to low-risk areas have a lower incidence of stomach cancer, environmental factors do indeed seem important. For example, it has been suggested that the high incidence in Iceland is due to ingested polycyclic hydrocarbons found in smoked meat and fish.[22] Undetermined environmental influences may also explain why stomach cancer is more common among poorer population groups in both Europe and North America.[27, 41]

However, there is some preliminary evidence of ethnic predisposition to carcinoma of the stomach which does not appear to be related to environmental factors. Several years ago, Legon[12, 13] called attention to a surprisingly high incidence of deaths due to stomach cancer in certain areas of Wales. In a recent epidemiological study, Ashley and Davies[6] noted that the distribution of gastric cancer followed closely the distribution of Welsh surnames, even in areas where Welsh and non-Welsh lived side by side with apparently similar environmental, occupational, and culinary conditions.

In addition to ethnic factors, there appear to be some families with a disproportionately high incidence of cancer. Often, these pedigrees exhibit a heterogeneity of type and location of neoplasms. However, in some of these families it appears that there is a particular propensity toward gastric cancer. Certainly, the fact that carcinoma of the stomach occurs more often in any given pedigree than would be expected by chance suggests that there may be a genetic background influencing acquisition of the disease. However, broad conclusions concerning cancer-susceptible genotypes must be made with caution because of the tendency to report only those families with a high incidence of cancer. In addition, gastric carcinoma is not uncommon, and random distribution of this disease may result in several cases in one family. Nevertheless, the familial aggregation of gastric carcinoma is considerable,[46, 78] and the incidence of gastric cancer has been reported to be approximately four times higher among the relatives of patients with this illness than in a control population.[67]

Studies of twins have suggested heritable factors in stomach cancer. Isolated case reports have described carcinoma of the stomach appearing in monozygous twins, although reported cases of nonconcordance are equally common.[25] However, it does appear that there is a greater concordance for cancer of the stomach in monozygous twin pairs than in dizygous twin pairs.[26] The results of this MZ-DZ comparison method[10] suggest that, although there are heritable constitutional factors favorable to gastric cancer, environmental modifying influences are also important.

Another factor influencing the incidence of gastric carcinoma is the high incidence of the latter among pernicious anemia patients. The heritable aspects of this latter disease have been amply documented.[14, 18]

A final factor of importance in the consideration of the multifactorial genetic influences upon gastric cancer relates to the discovery by Aird and co-workers[2] of the increased incidence of blood group A in patients with this disease. This relationship is true for areas of both high and low incidence, and has been confirmed by other investigators.[11, 52] How do the blood groups play a role in the susceptibility to, or the protection against, carcinoma of the stomach? Does the gene which determines the presence of blood group A have a pleiotropic effect, in that it may modify or enhance other genes which influence biochemical processes predisposing to carcinogenesis in the stomach? Does blood group A indirectly exert a toxic influence upon the stomach? The cellular ABO mucopolysaccharide antigens may occur in soluble form in saliva, and such persons are termed secretors. The ability to secrete these antigens is controlled by a secretor locus or loci. Initially, it was postulated that group A secretor substances may topically irritate the stomach and induce malignant change.[61] However, it appears that the secretor is not unduly predisposed to carcinoma of the stomach.[20] Other intriguing observations concerning blood group A which may have some relationship to gastric cancer are the apparent correlation of group A and gastric hypochlorhydria,[57, 62] and the association of group A and pernicious anemia.[30]

Polygenic influences also have been implicated in ulcerative colitis and regional enteritis,[4] and in duodenal ulcer.[58] Undoubtedly, there are many other gastrointestinal diseases in which polygenic inheritance factors will be found.

COMMENTS

It should be emphasized that, because of limitation of space, the foregoing discussion by no means includes a complete list of genetically determined gastrointestinal diseases. Also, in view of the relatively incomplete genetic knowledge concerning many gastrointestinal diseases, a complete listing is not possible. The reader who is particularly interested in this subject is referred to the several discussions and reviews which are available.[33, 45, 47, 50, 59]

The subdivisions created for the purpose of this discussion are intended merely to facilitate exposition of some of the aspects of genetic gastrointestinal disease; they should not be construed as an attempt at fundamental classification. Some of those diseases which have been referred to in the literature as being due to single genes or a pair of genes (alleles) have had insufficient pedigree studies, and may be found eventually to be dependent for their penetrance on the presence or absence of other alleles. Often, the characterization of the inheritance pattern as dominant or recessive is based upon limited data. Also, the distinction between a disease of function and one of structure is frequently unclear. It seems likely that future investigations will demonstrate that deficiencies or anomalies of enzyme protein are involved in the causation of some structural gastrointestinal diseases.

Hereditary factors are seldom clear-cut. The collection of accurate pedigree data in the human is fraught with difficulties and errors because of insufficient numbers of offspring on which to base mathematical ratios, long generation time, illegitimacy, secrecy, and misrepresentation. Our clinical and laboratory techniques are often insufficient to recognize phenotypic abnormality. Undiagnosed in-utero lethality, new mutations, sex limitation, and intermediate gene action further becloud the data and confuse our interpretations.[9] Heredity is to a greater or lesser extent concerned in the etiology of all diseases. However, there are few purely genetic diseases. Even those diseases predominantly determined by heredity are the product of the combined effect of several alleles, all of which are influenced by exogenous factors. The extent of the intricate and continuous interaction between the genotype and its environment obliges the genotype to play only a modified role in phenogenesis. The elucidation of that role is of vital concern to the gastroenterologist, whether he be working in the laboratory or the clinic.

REFERENCES

1. Abraham, J. M., Levin, B., Oberholzer, V. G., and Russell, A.: Glucose-galactose malabsorption. Arch. Dis. Child., *42*:592, 1967.
2. Aird, I., Bentall, H. H., and Roberts, J. A. F.: A relationship between cancer of the stomach and the ABO blood groups. Brit. Med. J., *1*:799, 1953.
3. Aldrich, R. A., Steinberg, A. G., and Campbell, D. C.: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics, *13*:133, 1954.
4. Almy, T. P., and Sherlock, P.: Genetic aspects of ulcerative colitis and regional enteritis. Gastroenterology, *51*:757, 1966.
5. Anderson, P. J., and Popper, H.: Changes in hepatic structure in Wilson's disease. Amer. J. Path., *36*:483, 1960.
6. Ashley, D. J. B., and Davies, H. D.: Gastric cancer in Wales. Gut, 7:542, 1966.
7. Ballard, H. S., Frame, B., and Hartsock, R. J.: Familial multiple endocrine adenoma-peptic ulcer complex. Medicine, *43*:481, 1964.
8. Becker, K. L.: Pedigree analysis. 1. Dominance, recessiveness and sex-linkage. Postgrad. Med., *40*:6, 1966.
9. Becker, K. L.: Pedigree analysis. II. Clinical discrepancies and limitations. Postgrad. Med., *40*:171, 1966.
10. Becker, K. L.: The twin-study method in medicine and genetics. Postgrad. Med., *41*:603, 1967.
11. Buckwalter, J. A., Wohlwend, C. B., Colter, D. C., Tidrick, R. T., and Knowler, L. A.: The association of the ABO blood groups to gastric carcinoma. Surg. Gynec. Obstet., *104*:176, 1957.
12. Buell, P., and Dunn, J. E., Jr.: Cancer mortality among Japanese issei and nisei of California. Cancer, *18*:656, 1965.
13. Butt, H. R., Anderson, V. E., Foulk, W. T., Baggenstoss, A. H., Schoenfield, L. J., and Dickson, E. R.: Studies of chronic idiopathic jaundice (Dubin-Johnson syndrome). II. Evaluation of a large family with the trait. Gastroenterology, *51*:619, 1966.

14. Callender, S. T., and Denborough, M. A.: A family study of pernicious anaemia. Brit. J. Haemat., *3*:88, 1957.
15. Childs, B., Sidbury, J. B., and Migeon, C. J.: Glucuronic acid conjugation by patients with familial nonhemolytic jaundice and their relatives. Pediatrics, 23:903, 1959.
16. Clayton, R. J., Iber, F. L., Ruebner, B. H. and McKusick. V. A.: Byler's disease: Fatal intrahepatic cholestasis in an Amish kindred. J. Pediat., 67:1025, 1965.
17. Cockayne, E. A.: The genetics of transposition of the viscera. Quart. J. Med., 7:479, 1938.
18. Crigler, J. F., Jr., and Najjar, V. A.: Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics, *10*:169, 1952.
19. Debré, R., Dreyfus, J.-C., Frezal, J., Labie, D., Lamy, M., Maroteaux, P., Schapira, F., and Schapira, G.: Genetics of haemochromatosis. Ann. Hum. Genet., *23*:16, 1958.
20. Doll, R., Drane, H., and Newell, A. C.: Secretion of blood group substances in duodenal, gastric and stomach ulcer, gastric carcinoma, and diabetes mellitus. Gut, 2:352, 1961.
21. Dukes, C. E.: Familial intestinal polyposis. Ann. Eugen., *17*:1, 1952.
22. Dungal, N.: The special problem of stomach cancer in Iceland with particular reference to dietary factors. J.A.M.A., *178*:789, 1961.
23. Farrar, T., and Chappell, F. W.: Severe gastrointestinal hemorrhage resulting from Recklinghausen's disease. Arch. Surg., *79*:106, 1959.
24. Gardner, E. J.: A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Amer. J. Hum. Genet., *3*:167, 1951.
25. Gorer, P. A.: The genetic interpretations of studies on cancer in twins. Ann. Eugenics, *8*:219, 1937-38.
26. Gorer, P. A.: Genetics of human cancer: A general survey of methods. Ann. N.Y., Acad. Sci., *71*:1189, 1958.
27. Graham, S., Levin, M. L., Lilienfeld, A. M., and Sheehe, P.: Ethnic derivation as related to cancer at various sites. Cancer, *16*:13, 1963.
28. Gross, J. B., Gambill, E. E., and Ulrich, J. A.: Hereditary pancreatitis. Description of a fifth kindred and summary of clinical features. Amer. J. Med., *33*:358, 1962.
29. Gross, J. B., Ulrich, J. A., and Jones, J. D.: Urinary excretion of amino acids in a kindred with hereditary pancreatitis and aminoaciduria. Gastroenterology, *47*:41, 1964.
30. Group study: An association between blood group A and pernicious anemia. A collective series from a number of centres. Brit. Med. J., 2:723, 1956.
31. Halvorsen, S., Pande, H., Loken, A. C., and Gjessing, L. R.: Tyrosinosis. A study of 6 cases. Arch. Dis. Child., *41*:238, 1966.
32. Hodgson, C. H., Burchell, H. B., Good, C. A., and Clagett, O. T.: Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula. Survey of a large family. New Engl. J. Med., *261*:625, 1959.
33. Iber, F. I., and Maddrey, W. C.: Familial hepatic diseases with or without cirrhosis. *In* Progress in Liver Disease, Volume 2. New York, Grune & Stratton, 1965, Chapter 20.
34. Isselbacher, K. J., Scheig, R., Plotkin, G. R., and Caulfield, J. B.: Congenital beta-lipoprotein deficiency: An hereditary disorder involving a defect in the absorption and transport of lipids. Medicine, *43*:347, 1964.
35. Jeghers, H., McKusick, V. A., and Katz, K. H.: Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. New Engl. J. Med., *241*:993, 1031, 1949.
36. Johnston, A. W., Warland, B. J., and Weller, S. D. V.: Genetic aspects of angiokeratoma corporis diffusum. Ann. Hum. Genet., *30*:25, 1966.
37. Kaijser, K. and Malmstrom-Groth, A.: Ano-rectal abnormalities as a congenital familial incidence. Acta Paediat., *46*:199, 1957.
38. Kekomaki, M., Visakorpi, J. K., Perheentupa, J., Saxen, L.: Familial protein intolerance with deficient transport of basic amino acids. An analysis of 10 patients. Acta Paediat. Scand., 56:617, 1967.
39. Kerry, K. R. and Townley, R. R. W.: Genetic aspects of intestinal sucrase-isomaltase deficiency. Aust. Paediat. J., *1*:223, 1965.
40. Krauss, A. N.: Familial extrahepatic biliary atresia. J. Pediat. 65:933, 1964.
41. Langman, M. J. S.: The epidemiology of gastrointestinal cancer. Gut, *8*:315, 1967.
42. Legon, C. D.: The aetiological significance of geographical variations in cancer mortality. Brit. Med. J., 2:700, 1952.
43. Legon, C. D.: Cancer in North Wales. Brit. Med. J., *1*:265, 1963.
44. Lowe, C. U., May, C. D., and Reed, S. C.: Fibrosis of the pancreas in infants and children. A statistical study of clinical and hereditary features. Amer. J. Dis. Child., 78:349, 1949.
45. Lynch, H. T., and Rentchnick, P., *in* Recent Advances in Cancer Research, Volume 12. New York, Springer Verlag, 1967.
46. Macklin, M. T.: Inheritance of cancer of the stomach and large intestine in man. J. Nat. Cancer Inst., *24*:551, 1960.
47. McConnell, R. B.: The Genetics of Gastro-intestinal Disorders. London, Oxford University Press., 1966.
48. McIntyre, P. A., Hahn, R., Conley, C. L., and Glass, B.: Genetic factors in predisposition to pernicious anemia. Bull. Johns Hopkins Hosp., *104*:309, 1959.

49. McKusick, V. A.: Heritable Disorders of Connective Tissue. St. Louis, C. V. Mosby Co., 1966.
50. McKusick, V. A.: Mendelian Inheritance in Man. Catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes. Baltimore, The Johns Hopkins Press, 1966.
51. Mielke, J. E., Becker, K. L., and Gross, J. B.: Diverticulitis of the colon in a young man with Marfan's syndrome. Gastroenterology, 48:379, 1965.
52. Mosbech, J.: ABO blood groups in stomach cancer. Acta Genet., *8*:219, 1958.
53. Nussbaumer, T., Plattner, H. C., and Rywlin, A.: Hémochromatose juvénile chez trois soeurs et un frère avec consanguinité des parents. J. Genet. Hum., *1*:53, 1952.
54. Peutz, J. L. A.: Over eenzeer merkwaardige, gecombineerde familiaire polyposis van de slijmoliezen van den tractus intestinalis met die van de neuskeelholte en gepaard met eigenaardige pigmentaties van huid-en slijmoliezen. Med. Maandschr. Geneesk., *10*:134, 1921.
55. Pierce, J. W., Creamer, B., and MacDermot, V.: Pharynx and oesophagus in dystrophia myotonica. Gut, 6:392, 1965.
56. Powell, L. W.: Iron storage in relatives of patients with haemochromatosis and in relatives of patients with alcoholic cirrhosis and haemosiderosis. Quart. J. Med., *34*:427, 1965.
57. Purohit, G. L., and Shukla, K. C.: Correlation of blood groups with gastric acidity in normals. Indian J. Med. Sci., *14*:522, 1960.
58. Remelli, L., Serra, A., and Gualandri, V.: Contributo allo studio delle basi genetiche dell' ulcera duodenale. Acta Genet. Med., *13*:369, 1964.
59. Scheuer, P. J., and Williams, R.: Genetic disorders of the liver. *In* Progress in Liver Disease, Volume 2. New York, Grune & Stratton, 1965, Chapter 19.
60. Sheldon, W.: Congenital pancreatic lipase deficiency. Arch. Dis. Child., *39*:268, 1964.
61. Sheppard, P. M.: Cancer of the stomach and ABO blood groups. Brit. Med. J., *1*:1220, 1953.
62. Sievers, M. L.: Hereditary aspects of gastric secretory function. Amer. J. Med., 27:246, 1959.
63. Suckling, P. V.: Familial incidence of congenital abnormalities of the anus and rectum. Arch. Dis. Child., *24*:75, 1949.
64. Szabo, L., Kovacs, Z., and Ebrey, P.: Congenital non-haemolytic jaundice. Lancet, *1*:322, 1962.
65. Van Gelder, D. W., and Kloepfer, H. W.: Familial anorectal anomalies. Pediatrics, 27:334, 1961.
66. Victor, M., Hayes, R., and Adams, R. D.: Oculopharyngeal muscular dystrophy. A familial disease of late life characterized by dysphagia and progressive ptosis of the eyelids. New Engl. J. Med., 267:1267, 1962.
67. Videback, A., and Mosbech, J.: The aetiology of gastric carcinoma elucidated by a study of 302 pedigrees. Acta Med. Scand., *149*:137, 1954.
68. Walker, F. A., Hsia, D. Y. Y., Slatis, H. M., and Steinberg, A. G.: Galactosemia. A study of 27 kindreds in North America. Ann. Hum. Genet., 25:287, 1962.
69. Waters, A. H., and Murphy, M. E. B.: Familial juvenile pernicious anemia: A study of the hereditary basis of pernicious anemia. Brit. J. Haemat., *9*:1, 1963.
70. Watson, C. J.: The problem of porphyria—some facts and questions. New. Engl. J. Med., *263*:1205, 1960.
71. Wefring, K. W., and Lamvik, J. O.: Familial progressive poliodystrophy with cirrhosis of the liver. Acta Paediat. Scand., *56*:295, 1967.
72. Weimer, B. R.: Congenital inheritance of inguinal hernia. J. Hered., *40*:219, 1949.
73. Weinstein, E. D.: Sex-linked imperforate anus. Pediatrics, 35:715, 1965.
74. Williams, R., Pitcher, C. S., Parsonson, A., and Williams, H. S.: Iron absorption in the relatives of patients with idiopathic haemochromatosis. Lancet, *1*:1243, 1965.
75. Williams, R., Scheuer, P. J., and Sherlock, S.: The inheritance of idiopathic haemochromatosis. Quart. J. Med., *31*:249, 1962.
76. Wilson, T. H.: Membrane transport of vitamin B_{12}. Medicine, *43*:669, 1964.
77. Woo, J. C., Jr., and Chandler, F. W.: Pseudoxanthoma elasticum with gastric hemorrhage: Report of a case. Ann. Intern. Med., *45*:215, 1958.
78. Woolf, C. M.: A further study on the familial aspects of carcinoma of the stomach. Amer. J. Hum. Gen., *8*:102, 1956.

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422

Autoimmune Mechanisms and the Gastrointestinal Tract

CHARLES A. HALL, M.D.[*]

Autoimmunity is an inexact designation for an ill-defined concept. In the most restricted sense, autoimmunity is the presence in a person of antibodies that react with his own cells or with their products. In the broader and more common use of the word, injury to the cells or their products by the antibody, and resulting clinical disease, are implied. Autoimmunity has not been proved to be a cause of disease, although there are instances in which such a mechanism probably causes manifestations of disease. In autoimmune hemolytic anemia, for example, antibodies are present that react with and injure the patient's own erythrocytes, and the disease is one of excessive destruction of erythrocytes. A causative relationship between autoantibody and disease is not the only possible explanation of the presence of antibodies. Autoantibody may be a *consequence* of damaged cells, not the cause. Autoantibody may be a manifestation of a disturbance of the immune system which also, but quite independently of the observed antibody, is the cause of the disease. In spite of much speculation and indirect evidence, the origin and significance of autoantibodies remain unknown.

Four types of observations suggest involvement of the immune system in the gastrointestinal tract diseases to be discussed. They are (1) the presence in the lesion of cells that can produce antibody; (2) an elevation of plasma gamma globulins; (3) association with diseases generally considered to involve autoimmunity; and (4) a beneficial response to adrenal corticosteroids.

Antibodies that react with cells of the gastrointestinal tract or with their products are observed in disease. Although in no instance is the significance of the antibody known, these antibodies are the best focus for a discussion of autoimmunity in respect to the gastrointestinal tract. The present discussion does not include all of the antibodies or situations of possible autoimmunity, only the major ones. A more inclusive presentation can be found in monographs on autoimmunity in general[33, 41] or pertaining to the gastrointestinal tract.[46]

Associate Chief of Staff, Veterans Administration Hospital; Professor of Medicine, Albany Medical College, Albany, New York

PARIETAL CELL ANTIBODY

Parietal cell antibody reacts with the parietal cells of gastric mucosa. It was first observed in pernicious anemia,[27, 17] and it has been found at a lower incidence in other diseases of probable autoimmunity.[27] The antibody is usually detected by either an immunofluorescent or a complement-fixing technique. It belongs to the IgG group of immunoglobulins,[29, 17] but there may be an IgA component as well,[17] although the latter has been disputed. The antigen is in the microsomal fraction of the cytoplasm of the gastric mucosal cell. The antibody reacts with gastric mucosa of several other species of animal; it does not, however, react with cytoplasm of cells from other parts of the human gastrointestinal tract.[17] It is in the gastric juice as well as the serum, although not as often and in lower titer.[17, 29]

While the sera of more than three fourths of all pernicious anemia (PA) patients have the antibody, its incidence is not confined to these patients. An incidence above control level occurs in Hashimoto's thyroiditis, spontaneous myxedema, thyrotoxicosis, diabetes mellitus, and idiopathic hypoadrenalism.[14, 28] Other than in PA, the greatest incidence of parietal cell antibody is in various types of thyroid disease. The data given in Table 1 are representative. Two different measures of parietal cell antibody, a test for antibody against thyroid cytoplasm, and a test for antithyroglobulin are all given in the table. It is interesting to note that both types of antithyroid antibodies are increased in PA and that many patients with either PA or thyroid disease have antibodies against both thyroid and parietal cells. A few patients have diseases involving both the thyroid and the stomach. Relatives of patients with either disease have an increased incidence of both antibodies.[15] The nature of this rela-

Table 1. *The Incidence of Gastric and Thyroid Antibodies in Addisonian Pernicious Anemia, Thyroid Disease, and Control Subjects**

		PER CENT WITH POSITIVE TESTS			
		I.C. FOR GASTRIC PARIETAL CELLS	C.F. (≥ 1:4) FOR		
	NO.		BODY OF STOMACH	THYROID	T.C.H. (≥1:5)
Pernicious anemia	108	76	63	27	26
Hashimoto's thyroiditis	64	25	20	83	78
Spontaneous hypothyroidism	139	33	25	58	70
Thyrotoxicosis	302	24	17	34	32
Simple goiter	64	3	3	5	12
Hospital controls	372	8	6	3	9
Blood donors	629	5	3	4	9

I.C., indirect Coombs' fluorescent antibody method.

C.F., complement fixation using 2.0 M.H.D. of complement, reading at 50 per cent hemolysis.

T.C.H., tanned cell hemagglutination test for antibody to thyroglobulin.

*Modified from Irvine, W. J., Davies, S. H., Teitelbaum, S., Delamore, I. W., and Williams, A. W., Ann. N.Y. Acad. Sci., *124*:661, 1965.

tionship between a disease of the parietal cells (PA) and one of the thyroid cells remains unknown.

Persons with gastritis but without pernicious anemia have an increased incidence of parietal cell antibody. Previous studies and current thinking are summarized in a recent editorial.[16] When parietal cell antibody is present, the gastric mucosa is almost always, if not always, abnormal to some extent. The greater the degree of gastric abnormality, the greater the incidence of antibody. Some patients with atrophic gastritis, achlorhydria, and antibody have PA, while others do not—that is, their parietal cells secrete intrinsic factor. Similar degrees of gastritis are seen in persons who have no antibody.

The antibody is found in some persons with iron deficiency and gastritis. Probably there are two variants of this latter combination.[13] One is an idiopathic, chronic gastritis with iron deficiency probably as a secondary manifestation; antibody is sometimes present. The other type is a gastritis secondary to iron deficiency of a known cause, usually hemorrhage; antibody is not present.

The origin and consequence of parietal cell antibody and its relationship to disease are unknown. The detection of the antibody is of no value in diagnosis, since it is found in several situations and not in all cases of any one disease.

INTRINSIC FACTOR (IF) ANTIBODIES

Sera from over half of all persons with pernicious anemia contain one or both of two autoantibodies that react with intrinsic factor. I will give only the more recent references to this observation; the earlier work must be interpreted in the light of the new, and two recent reports contain excellent, complete bibliographies.[7, 42] The type of IF antibody made by injecting human IF into animals and the type that follows oral intake of porcine IF are not discussed.

There are two distinct IF antibodies, which react with two different sites on the IF molecule.[20, 42, 43] These are identified as Types I and II,[42] or more commonly as "blocking" and "precipitating" antibody. Incidence and mode of action of these antibodies are given in Table 2. The study illustrated is representative of the more general experience. Type I antibody, the most common and the one most often measured, blocks the

Table 2. *Antibodies Found in Pernicious Anemia (PA) Plasma**

TYPE	INCIDENCE IN PA (PER CENT)†	POINT OF ACTION	BLOCKS B_{12} ABSORPTION WHEN SEQUENCE IS:
I	53	B_{12} binding to IF	IF + Antibody + B_{12}
II	34	IF-B_{12} Complex	IF + B_{12} + Antibody

*From Schade, S. G., Abels, J., and Schilling, R. F., J. Clin. Invest., 46:615, 1967.

†47 per cent of sera had no antibodies, 34 per cent had both. Type II did not occur in the Absence of Type I.

binding of vitamin B_{12} to IF. It also exchanges with the B_{12} of IF-B_{12} complex.[43] The term "blocking," sometimes used for this antibody, refers to its action. It inhibits the function of IF (necessary in absorption of B_{12}) when added to the IF *before* the B_{12}. Type II antibody reacts with the IF-B_{12} complex or with IF alone.[20, 43] The reacting substances form a precipitate – hence one of the names for antibody II. This antibody inhibits the in vivo function of IF when added to the IF-B_{12} complex.

Types I and II are serum antibodies, but are found in gastric juice as well.[12, 18, 44] Both belong to the IgG class of immunoglobulins. Type I is not species-specific, reacting with human, porcine, monkey, and rat IF.[45] A study of the structure of both[7] has shown that, like normal immunoglobulins, the IF antibodies are heterogeneous in structure. This suggests that they arise from a stimulus to a normally functioning immune system. Were they homogeneous, a monoclonal origin would be suggested – that is, they might be analogous to a paraprotein in the gammopathies.

A few instances of intrinsic factor antibody in the absence of PA have been reported.[4, 26, 49] The exceptions occur in persons with other autoimmune disease and associated with gastric atrophy and achlorhydria. With sufficient time of observation, these exceptions may be found to develop PA. Antibodies are not found in sera of patients with juvenile PA.[15] The reasons why not all patients with PA have IF antibody are still unknown. One investigation[12] suggested that if both antibodies are sought in more than one body fluid, the incidence may be higher than previously suspected. The presence or absence of antibody does not correlate with the severity of disease, its duration, or with any set of manifestations. A possible exception is the demonstration of absent IF antibody in the most severe degrees of gastric atrophy in PA.[45] The antibody persists unreduced after successful treatment with B_{12}.

Neither the cause nor the consequences of the presence of antibody in the serum or gastric juice are known. There is no evidence to suggest that either type of IF antibody has a part in either the cause or the pathogenesis of PA. Type II antibody in gastric juice can inhibit B_{12} absorption.[14] Schwartz[15] showed that serum IF antibody (type unidentified) interfered with IF activity in a patient whose IF production was reduced by partial gastrectomy. If, then, a patient with PA has some small residual of IF production, any antibody in gastric juice or saliva could further impair B_{12} absorption.

Adrenal corticosteroids change the manifestations of pernicious anemia. Chief and parietal glands may return to the gastric mucosa, acid and IF production may recover to a degree, and B_{12} absorption improves.[3, 30] Intrinsic factor antibodies in the serum persist but the titer may fall somewhat.[3, 30, 45] Parietal cell antibody persists unchanged.[30]

Detection of IF antibody is almost always, if not always, diagnostic of PA. Were the incidence in serum high enough, the antibody would be valuable in diagnosis. Even with the many negative sera, there may be situations in which the presence of antibody is helpful. Since antibody persists in spite of treatment or status of the PA, the detection of it may be a simple test for PA in a stage when many other tests have reverted to normal.

Type I antibody in serum is measured by adding radioactive B_{12} to human IF and determining the amount of binding blocked by the serum. This requires separation of free and bound B_{12}, often accomplished by dialysis, gel filtration, adsorption of free B_{12} to charcoal, or adsorption of bound B_{12} to zirconyl gel phosphate. Tests for Type II antibody are based on alteration of the properties of IF-B_{12}, such as electrophoretic mobility, or on the precipitate formed when the antibody combines with IF-B_{12}. Type I antibody is easier to measure; it occurs in the absence of Type II, while the reverse is rarely if ever found. Type I is, therefore, the one usually sought for. A test using charcoal to separate free and bound B_{12} probably will prove to be the most useful.[22]

Intrinsic factor itself can be measured through the use of Type I IF antibody. Although this procedure has not had wide clinical use, the potentials are great. The absence or near absence of IF from gastric juice is pathognomonic of all clinical variants of PA (excepting that rare type of "juvenile PA" which is unrelated to PA and in which the defect of B_{12} absorption is in the ileum). This basic lesion persists after treatment. Any person who cannot produce IF will develop clinical PA once his body B_{12} is depleted. Therefore, measurement of IF in gastric juice can either make or exclude the diagnosis of PA.

Although there are several ways of measuring IF, the method based on IF autoantibody is the simplest. The principles are also simple. Gastric juice contains more than one binder of B_{12}. However, Type I antibody from PA serum blocks only the part of gastric juice binding that originates from the IF. The degree of B_{12} binding of gastric juice that is blocked by antibody is, therefore, a measure of the amount of IF present. The gastric juice is collected after maximum stimulation with histamine; radioactive B_{12} is added; and B_{12} binding is measured by adsorbing the free B_{12} as with charcoal. The test has been successfully applied in diagnosis.[2, 22]

ANTIBODIES IN LIVER DISEASE

Antibodies are commonly part of the syndrome only in some of the less common types of liver disease. This restriction of the occurrence of antibodies may, in fact, give greater significance to the few situations in which they are found than would the presence of antibodies in many types of liver injury.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is a rare disease seen mostly in women. Antibody against liver tissue has been found in a larger percentage of sera from these cases than in any other type of liver disease;[21, 50] the incidence was 100 per cent in one study. Most investigators used a complement fixation test to detect the anticytoplasmic antibody, but immunofluorescence may be more sensitive.[50] As will be shown, the anticytoplasmic antibody, as seen in various liver diseases, is never organ-specific. Its incidence is not confined to liver disease,[23] nor is it species-specific. Paronetto et al.[38] found large amounts of IgM in the basophilic mesenchymal cells of the lesion, in contrast to IgG found in related cells of hepatic lesions of other diseases. The anticytoplasmic antibody occurs in other liver diseases, although some have found the incidence to be very low.[21, 50] More information is needed for a firmer classification of the antibody, and its significance is completely unknown. Possibly, it could be useful in diagnosis, since the incidence is nil in extrahepatic biliary obstruction.[21, 50] One observer[38] described a second antibody, one against bile duct cells. There are other abnormalities of immunity in primary biliary cirrhosis; nonspecific antinuclear factors are often found in the blood and, in some cases, so is the rheumatoid factor.

Lupoid Hepatitis

Autoimmunity may be associated with another form of chronic liver disease, lupoid hepatitis. This is a disease or perhaps a syndrome, chiefly in young women, with features of both hepatitis and systemic lupus erythematosus (SLE).[6, 34] The liver disease is chronic and progressive and ultimately resembles postnecrotic cirrhosis. Arthralgia, fever, pleurisy, and rashes are common. By definition, the LE test is positive; it is not as strongly or as persistently positive as in SLE. Lupoid hepatitis is a difficult disease to classify. Possibly it is a variant of the more usual type of chronic hepatitis but with various autoimmune phenomena superimposed. It is more likely, but far from demonstrated, that it is a variant of SLE, with prominent hepatic disease but with the common manifestations of SLE fewer or less pronounced. Hepatic involvement is neither common nor severe in the usual SLE, but lupoid hepatitis could be an expression of the abnormality of SLE in the liver rather than in the more usual tissues.

Antinuclear factors, although nonspecific, are found in lupoid hepatitis. Some patients have complement-fixing antibodies against cytoplasmic liver antigen in the serum and the incidence is higher than in most other liver diseases.[34] The antibody, like that seen in primary biliary cirrhosis, is neither organ-specific nor species-specific.[19] The antibody is also seen in SLE without the hepatic aspect.[19, 21] An antibody against smooth muscle has been observed in sera from patients with lupoid hepatitis, but not in that from SLE or related diseases.[31]

Lupoid hepatitis responds to adrenal corticosteroids,[31] further suggesting an autoimmune relationship. The degree of response is variable and the patient often relapses when treatment is discontinued.

Other Liver Diseases

Knowing that two forms of chronic liver disease, lupoid hepatitis and primary biliary cirrhosis, may belong in the autoimmune group of diseases, the possibility that others do must be considered. Lymphocytes are common in the lesions of other forms of cirrhosis and the plasma gamma globulins are often elevated. The chronic hepatitis that rarely follows viral hepatitis progresses long after the presence of virus is likely and an autoimmune reaction could be the basis for the continuing disease. The incidence of nonspecific cytoplasmic antibodies in the serum in chronic active hepatitis or postnecrotic cirrhosis varies widely.[19, 21, 31]

Even those reporting antibodies found them in much lower titer than in lupoid hepatitis and primary biliary cirrhosis.[19] Both the incidence of antibody and, when present, the titer tend to be low in acute hepatitis.[19, 21, 50] Anticytoplasmic antibody is uncommon in alcoholic or Laennec's cirrhosis;[21, 34] when seen, the titer is low.[19]

Many of the drugs that injure the liver probably do so through some sort of hypersensitivity. Sometimes fever, rash, or arthralgia further suggest a hypersensitivity reaction. Attempts to find a circulating antibody have been disappointing. Possibly, current techniques are not adequate to detect the antibody of this special situation.

ULCERATIVE COLITIS

The antibody in the serum of patients with ulcerative colitis is anticolon. It is detected by precipitation reactions, by hemagglutinin tests and by immunofluorescence. The incidence in sera tested by the first two techniques is usually high.[5, 8, 9] In one study, however, antibodies against rat feces antigen as detected by hemagglutination were no more common than in controls, 31 per cent.[35] Immunofluorescence is less sensitive, or perhaps more specific, and half or fewer of sera react.[10, 24, 32, 35] Antibody is found in both childhood and adult types of the disease, but both the incidence and the titer is higher in the former.[5] The antibody has never been found to be related to the severity or extent of the disease; it is even present post colectomy.[24] Reported differences in the incidence of antibody may be largely due to differences in the antigen used, in technique, and in reporting results.

There is much evidence that the antibody is a gamma globulin. Recently it has been identified in the IgG component of immunoglobulins.[24, 35] One study suggested the presence of a macroglubulin as well.[32] The antibody is not specific for cells or antigen of the colon. Hemagglutination and precipitation reactions occur between serum of ulcerative colitis and liver and kidney extracts prepared from tissue of human and other sources.[5, 9] Fluorescent staining in the presence of antibody is seen in the mucosa of small intestine as well as in the colon.[24, 36] By this technique there is staining of the same cells in animals, but there is not complete agreement as to which species react.[24, 36] The antigen, as measured by the fluorescent reaction, seems to be confined mainly to cells of the small or large intestine;[24, 36] the few exceptions are in cells in other parts of the gastrointestinal tract, stomach, and bile duct.[24, 32, 36] It is not always possible to claim that the antibody is an autoantibody; but reaction between the antibody and autologous tissue has been shown in a few cases.[24, 35]

The location of fluorescent staining reactions in the secretory region of the mucosal cell[24, 32, 36] may suggest certain origins of the antigen, but there is little exact information as to either origin or nature. It is probably an acid mucopolysaccharide;[32, 36] like antibody to intrinsic factor and to thyroglobulin, the antibody in ulcerative colitis may react against a cell product rather than to a part of the cell. Even a bacterial origin of the antigen has been suggested. Sterile, fetal colon is a preferred source of antigen in order to avoid bacterial antigens. The fact that serum antibodies in ulcerative colitis react with sterile colon does not exclude the possibility that bacteria were involved in the production of the antibody. Bacterial and colonic cells may share an antigen. The antigen is not the blood group substance H[10, 11] or A.[35]

Anticolon antibodies are not the only antibodies found in the sera of patients with ulcerative colitis. As noted above, there are antibodies reacting with liver and other tissues. The antibody against other tissues as reported in some studies is identical to the anticolon antibody; the antibody giving fluorescent staining with cells of both large and small intestine is an example. In other studies it is not always clear whether there is one nonspecific antibody or several more specific ones in the serum. The incidence of thyroid and parietal cell antibodies is not greater than in controls.[25] Antinuclear factors have been found in serum from ulcerative colitis by some,[48] but not by others.[25] The differences may be in technique, since those reporting positive results found only low titers. A few patients show the LE phenomenon.[1] These patients have symptoms of SLE and several of the reported cases had liver disease as well.

The anticolon antibody is not found in normal persons.[5, 8, 24] By the more sensitive techniques,[5, 8] it has been observed in SLE, rheumatoid arthritis, nephrosis, lupoid hepatitis, primary biliary cirrhosis, and other cirrhoses. The anticolon antibodies in ulcerative colitis and in rheumatoid arthritis are not the same.[10] Unsuccessful attempts have been made to connect ulcerative colitis with regional enteritis through a common antibody.[8, 32]

The cause of the serum antibodies in ulcerative colitis is completely unknown and there is no evidence indicating that they cause the disease. The nonspecificity of the antibodies, their occurrence in other diseases, and a definite incidence in less than half of the cases, weaken the case for a causal relationship. The colon is capable of reacting in an immune process, but it has not been possible to so produce a disease like ulcerative colitis in experimental animals. The ulcerated colon can admit all sorts of antigens into the circulation, including those in foods, blood, and bacteria. Antibodies against them may be produced, but so far there is no good evidence that the observed antibodies originate in this way. There are antibodies against milk proteins in the serum of persons with ulcerative colitis, and milk may aggravate symptoms of the disease. Milk antibodies, however, are found in normal persons and in many diseases.[10] Moreover, intolerance to milk is no proof of hypersensitivity of an immune type; milk may be poorly tolerated because of lactase deficiency. The anticolon antibody has not been shown to be injurious. The serum antibody as studied by Broberger and Perlmann did not injure colon cells in tissue culture.[11] Leukocytes from ulcerative colitis patients did, however, injure cells;[39] the role of antibody in the reaction was not clear. In trying to find a role for the antibodies in ulcerative colitis, one must consider that they may not have the same role in all ulcerative colitis. The disease is not a uniform one. A small percentage of cases may have an autoimmune basis, whereas the majority do not. A possible analo-

Table 3. *Properties of the More Specific Natural Antibodies Observed in Gastrointestinal Tract Disease*

ANTIBODY	REACTS WITH	SPECIFICITY		INCIDENCE	CLASS
		ORGAN OR SUBSTANCE	SPECIES		
Parietal cell	Parietal cell	Yes	No	¾ PA sera PA gastric juice Misc. disease	IgG
Intrinsic factor (IF)					
Type I	IF (blocks B_{12})	Yes	No	½ PA sera PA gastric juice	IgG
Type II	IF–B_{12} or IF	Yes	–	⅓ PA sera PA gastric juice	IgG
Anticolon (As detected by fluorescence)	An acid mucopolysaccharide	No*	No	⅓–½ ulcerative colitis sera	IgG

*Immunofluorescent staining of cells of small and large intestine. Lesser incidence and degree with gastric or bile duct mucosa.

gy is seen in chronic liver disease, where there is much more evidence for autoimmunity in two uncommon variants than in the more common varieties.

The antigen reacting with anticolon antibody in the immunofluorescent reaction may be absent from malignant cells of the colon.[24, 32, 37] Benign polyps stained normally,[37] but those with malignant features did not stain or only in a few cells. The loss of the antigen with the change from a benign to a malignant cell may be in some way related to a loss of mucus secretion.[24, 37]

SUMMARY

Some diseases of the gastrointestinal tract show evidence of a disturbed immune system. The most concrete facts are the presence of antibodies that react with gastrointestinal tract cells or their products. The more important, the more specific, and those sufficiently studied to be called antibodies are summarized in Table 3. Of these only Type I antibody to intrinsic factor has achieved practical usefulness; its presence is diagnostic of pernicious anemia and it is used in the assay of intrinsic factor.

REFERENCES

1. Alarcon-Segovia, D., Herskovic, T., Dearing, W. H., et al.: Lupus erythematosus cell phenomenon in patients with chronic ulcerative colitis. Gut, 6:39, 1965.
2. Ardeman, S., and Chanarin, I.: Assay of gastric intrinsic factor in the diagnosis of addisonian pernicious anemia. Brit. J. Haemat., *11*:305, 1965.
3. Ardeman, S., and Chanarin, I.: Steroids and addisonian pernicious anemia. New Eng. J. Med., *273*:1352, 1965.
4. Ardeman, S., Chanarin, I., Krafchik, B., and Singer, W.: Addisonian pernicious anemia and intrinsic factor antibodies in thyroid disorders. Quart. J. Med., *35*:421, 1966.

5. Asherson, G. L., and Broberger, O.: Incidence of haemogglutinating and complement-fixing antibodies. Brit. Med. J., *1*:1429, 1961.
6. Bartholomew, L. G., Hagedorn, A. B., Cain, J. C., and Baggenstoss, A. H.: Hepatitis and cirrhosis in women with positive clot tests for lupus erythematosus. New Eng. J. Med., *259*:947, 1958.
7. Bernier, G. M., and Hines, J. D.: Immunologic heterogeneity of autoantibodies in patients with pernicious anemia. New Eng. J. Med., 277:1386, 1967.
8. Bregman, E., and Kirsner, J. B.: Increased absorption of abnormal serum globulins in ulcerative colitis and other diseases. Amer. J. Clin. Path., *42*:368, 1964.
9. Broberger, O., and Perlmann, P.: Autoantibodies in human ulcerative colitis. J. Exp. Med., *110*:657, 1959.
10. Broberger, O., and Perlmann, P.: Demonstration of an epithelial antigen in colon by means of fluorescent antibodies from children with ulcerative colitis. J. Exp. Med., *115*:13, 1962.
11. Broberger, O., and Perlmann, P.: In vitro studies of ulcerative colitis. I. Reactions of patient's serum with human fetal colon cells in tissue cultures. J. Exp. Med., *117*:705, 1963.
12. Carmel, R., and Herbert, V.: Presence of "precipitating" or "blocking" antibody to intrinsic factor in gastric juice or serum of nearly all pernicious anemia patients. Clin. Res., *14*:482, 1966.
13. Delamore, I. W., and Shearman, D. J.: Chronic iron-deficiency anemia and atrophic gastritis. Lancet, *1*:889, 1965.
14. Doniach, D., Roitt, I. M., and Taylor, K. B.: Autoimmune phenomena in pernicious anemia. Brit. Med. J., *1*:1374, 1963.
15. Doniach, D., Roitt, I. M., and Taylor, K. B.: Autoimmunity in pernicious anemia and thyroiditis; A family study. Ann. N.Y. Acad. Sci., *124*:605, 1965.
16. Editorial: Parietal cell antibody and gastritis. Lancet, *1*:643, 1966.
17. Fisher, J. M., Rees, C., and Taylor, K. B.: Antibodies in gastric juice. Science, *150*:1467, 1965.
18. Fisher, J. M., Rees, C., and Taylor, K. B.: Intrinsic factor antibodies in gastric juice of pernicious anemia patients. Lancet, *1*:88, 1966.
19. Gajdusek, D. C.: An "autoimmune" reaction against human tissue antigens in certain acute and chronic diseases. I. Serological investigations. Arch. Int. Med., *101*:9, 1958.
20. Garrido-Pison, G. C., Turner, M. D., Crookston, J. H., Samloff, I. M., Miller, L. L., and Segal, H. L.: Studies of human intrinsic factor autoantibodies, J. Immun., *97*:897, 1966.
21. Gokcen, M.: Autoimmunity in liver disease. J. Lab. Clin. Med., *59*:533, 1962.
22. Gottlieb, C., Lau, K-S., Wasserman, L. R., and Herbert, V.: Rapid charcoal assay for intrinsic factor (IF), gastric juice unsaturated B_{12} binding capacity, antibody to IF, and serum unsaturated B_{12} binding capacity. Blood, 25:875, 1965.
23. Hackett, E., Beech, M., and Forbes, I. F.: Autoimmune complement-fixation reaction in 1014 patients. Brit. Med. J., 2:17, 1960.
24. Harrison, W. J.: Autoantibodies against intestinal and gastric mucous cells in ulcerative colitis. Lancet, *1*:1346, 1965.
25. Harrison, W. J.: Thyroid, gastric (parietal-cell), and nuclear antibodies in ulcerative colitis. Lancet, *1*:1350, 1965.
26. Irvine, W. J.: Immunolgic aspects of pernicious anemia. New Eng. J. Med., *273*:432, 1965.
27. Irvine, W. J., Davies, S. H., Delamore, I. W., and Williams, A. W.: Immunological relationship between pernicious anemia and thyroid disease. Brit. Med. J., 2:454, 1962.
28. Irvine, W. J., Davies, S. H., Teitelbaum, S., Delamore, I. W., and Williams, A. W.: The clinical and pathological significance of gastric parietal cell antibody. Ann. N.Y. Acad. Sci., *124*:657, 1965.
29. Jeffries, G. H., and Sleisenger, M. H.: Studies of parietal cell antibody in pernicious anemia. J. Clin. Invest., *44*:2021, 1965.
30. Jeffries, G. H., Todd, J. E., and Sleisenger, M. H.: The effect of prednisolone on gastric mucosal histology, gastric secretion and vitamin B_{12} absorption in patients with pernicious anemia. J. Clin. Invest., 45:803, 1966.
31. Johnson, G. D., Holborow, E. J., and Glynn, L. E.: Antibody to smooth muscle in patients with liver disease. Lancet, 2:878, 1965.
32. Koffler, D., Minkowitz, S., Rothman, W., and Garlock, J.: Immunocytochemical studies in ulcerative colitis and regional ileitis. Amer. J. Path., *41*:733, 1962.
33. MacKay, I. R., and Burnet, F. M.: Autoimmune Disease. Springfield, Ill., Charles C Thomas, 1964.
34. MacKay, I. R., and Wood, I. J.: Lupoid hepatitis: A comparison of 22 cases with other types of liver disease. Quart. J. Med., *31*:485, 1962.
35. McGiven, A. R., Ghose, T., and Nairn, R. C.: Autoantibodies in ulcerative colitis. Brit. Med. J., 2:19, 1967.
36. Nairn, R. C., Fothergill, J. E., McEntegart, M. G., and Porteous, I. B.: Gastrointestinal specific antigen: An immunological and serological study. Brit. Med. J., *1*:1788, 1962.

37. Nairn, R. C., Fothergill, J. E., McEntegart, M. G., and Richmond, H. G.: Loss of gastrointestinal specific antigen in neoplasia. Brit. Med. J., *1*:1791, 1962.
38. Paronetto, F., Schaffner, F., and Popper, H.: Immunocytochemical and serological observation in primary biliary cirrhosis. New Eng. J. Med., *271*:1123, 1964.
39. Perlmann, P., and Broberger, O.: In vitro studies of ulcerative colitis. II. Cytotoxic action of white blood cells from patients on human fetal colon cells. J. Exp. Med., *117*:717, 1963.
40. Peterson, R. D. A., and Good, R. A.: Antibodies to cow's milk proteins – their presence and significance. Pediat., *31*:209, 1963.
41. Samter, M., ed.: Immunological Diseases. Boston, Little, Brown and Co., 1965.
42. Schade, S. G., Abels, J., and Schilling, R. F.: Studies on antibody to intrinsic factor. J. Clin. Invest., *46*:615, 1967.
43. Schade, S. G., Feick, P. L., Imrie, M. H., and Schilling, R. F.: In vitro studies on antibodies to intrinsic factor. Clin. Exp. Immunol., *2*:399, 1967.
44. Schade, S. G., Feick, P., Muckerheide, M., and Schilling, R. F.: Occurrence in gastric juice of antibody to a complex of intrinsic factor and vitamin B_{12}. New Eng. J. Med., 275:528, 1966.
45. Schwartz, M.: Antibody to intrinsic factor. Scand. J. Clin. & Lab. Invest., *19*:19 (Suppl. 95.), 1967.
46. Taylor, K. B.: Progress in gastroenterology; immunological mechanisms of the gastrointestinal tract. Gastro., *51*:1058, 1966.
47. Taylor, K. B., Roitt, I. M., Doniach, D., Couchman, K. G., and Shapland, C.: Autoimmune phenomena in pernicious anemia: Gastric antibodies. Brit. Med. J., 2:1347, 1962.
48. Thayer, W. R., Calabresi, P., and Spiro, H. M.: Further observations on the antinuclear globulin in ulcerative colitis and regional ileitis. Gastro., *40*:695, 1961.
49. teVelde, K., Hoedemaeker, P. J., Anders, G. J. P. A., Arends, A., and Nieweg, H. O.: A comparative morphological and functional study of gastritis with and without autoantibodies. Gastro., *51*:138, 1966.
50. Walker, F. C., Doniach, D., Roitt, I. M., and Sherlock, S.: Serological tests in diagnosis of primary biliary cirrhosis. Lancet, *1*:827, 1965.

Veterans Administration Hospital
113 Holland Avenue
Albany, New York 12208

Gastrointestinal Hormones

MORTON I. GROSSMAN, M.D., Ph.D.*

The gastrointestinal hormones are polypeptides produced by the mucosa of the distal portion of the stomach and proximal small intestine. They take part in regulating the secretory and motor activities of the stomach, small intestine, pancreas, liver, and biliary tract.

Endocrine glands of mesodermal origin embryologically produce steroid hormones; those of ectodermal or endodermal origin, including the gastrointestinal mucosa, produce hormones composed of amino acids or derivatives of amino acids.

Establishing the existence of a gastrointestinal hormone requires these steps: (1) the physiological demonstration that a stimulus applied to one gastrointestinal structure alters the activity of another structure or another portion of the same structure; (2) the physiological demonstration that this effect persists when all nervous connections between the point of application of the stimulus and the responding tissue have

Table 1. *Gastrointestinal Hormones Established by Physiological and Chemical Criteria*

HORMONE	SITE OF PRODUCTION	TARGET AND ACTION[a]	DISCOVERED BY (YEAR)	PROOF OF EXISTENCE	
				Physiological[b]	*Chemical*
Gastrin	Pyloric gland area of gastric mucosa	Oxyntic glands of stomach; stimulates H^+ secretion	Edkins (1905)[11]	+	+
Secretin	Small intestinal mucosa	Pancreas; stimulates HCO_3^- secretion	Bayliss & Starling (1902)[1]	+	+
Pancreozymin	Small intestinal mucosa	Pancreas; stimulates enzyme secretion	Harper & Raper (1943)[21]	+	±[c]
Cholecystokinin	Small intestinal mucosa	Gallbladder; contraction	Ivy & Oldberg (1928)[22]	+	±[c]

[a] The action listed is the main one on which discovery of the hormone was based. Additional actions of the pure hormones have been demonstrated.

[b] Physiological proof of hormonal status requires that the substance be shown to play a role in normal regulation of activity and not merely to alter the activity of a gastrointestinal organ.

[c] Pancreozymin-cholecystokinin has been isolated as a single pure polypeptide,[28] but the sequence of amino acids has not yet been fully established.

---

[*] Professor of Medicine and Physiology, University of California School of Medicine; Senior Medical Investigator, Veterans Administration Center, Los Angeles, California

been eliminated; (3) the isolation from the site of application of the stimulus of a substance that mimics the physiological action; and (4) chemical identification of the substance and proof of its structure by synthesis.

This review will deal only with the three hormones listed in Table 1; these fulfill all or nearly all the criteria listed. Other putative gastrointestinal hormones and related substances include enterogastrone,[16] duocrinin,[9] villikinin,[25] enterocrinin,[29] antral chalone,[34] urogastrone,[18] gastrone,[6] and insulin-releasing hormone.[23]

GASTRIN

Gastrin has been isolated from the antral mucosa of four species, man, hog, dog, and sheep.[20] In all of these species gastrin is a polypeptide with 17 amino acid residues; the differences between gastrins from various species consist of substitution of one or two of the 17 residues (Fig. 1). In all species gastrin occurs in two forms, gastrin I without and gastrin II with ethereal sulfate on the ring of tyrosine in position 12. Although the two gastrins have different physicochemical properties, they apparently do not differ in biological activity, but this deserves more study.

The gastrins of all species studied to date have the same C-terminal tetrapeptide amide, -Try-Met-Asp-Phe-NH_2. This portion of the molecule can be regarded as the active center; it has all the biological activities of the full molecule, but is about one fifth as potent on a weight basis or about one twentieth on a molar basis. Many peptides related to the active tetrapeptide have been synthesized. A few have slight to moderate gastrin-like activity, but none has yet been found to be an antagonist of gastrin.[27] The compound most widely available for use in human subjects and animals is N-t-butyloxycarbonyl-β-Ala-Try-Met-Asp-Phe-NH_2. In human subjects 6 μg. per kg. body weight intramuscularly produced rates of acid secretion about equal to those attained with maximal doses of histamine.[24] The claim that this pentapeptide is more potent than the C-terminal tetrapeptide has not been validated.[8] A synthetic substituted thioacetamide that slightly resembles phenylalanine, the C-terminal amino acid of gastrin, has been shown to inhibit acid secretion stimulated by gastrin in dogs.[2]

Gastrin is produced by the mucosa of the pyloric gland area of the

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Man	Glu-	Gly-	Pro-	Try-	Leu-	Glu-	Glu-	Glu-	Glu-	Glu-	Ala-	Try-	Gly-	Try-	Met-	Asp-	Phe-NH_2
Hog					Met												
Dog						(Ala)											
Sheep					Val-	(Ala)											

Figure 1. Structure of gastrin from several species. The N-terminal residue is in the pyroglutamyl form. In dog and sheep gastrins the *Ala* is in parentheses to indicate that it is not yet known which glutamyl residue (6-10) is replaced by alanyl.

stomach, the portion that does not secrete acid. The cells that produce gastrin have not been identified. It is assumed that the boundary between acid-secreting and non-acid-secreting mucosa is the same as the boundary between non-gastrin-producing and gastrin-producing mucosa. However, this assumption has not been critically tested, because methods for extraction and assay of gastrin are not sufficiently sensitive. Some have assumed that areas that undergo metaplasia and lose the ability to secrete acid, such as the area surrounding a gastric ulcer or the area near a gastroenterostomy stoma, also acquire the ability to produce gastrin. These speculations have not been tested by direct measurement of the gastrin content of such tissues.

Certain foods and their partial digestion products stimulate gastric secretion when present in the upper small intestine, even when all nerves between intestine and stomach have been cut.[15] This suggests the existence of an "intestinal gastrin." Whether this "intestinal gastrin" has the same chemical structure as antral gastrin is at present unknown. One interesting possibility is that cholecystokinin-pancreozymin (CCK-PZ) may be the "intestinal gastrin" or one of a group of "intestinal gastrins." Highly purified CCK-PZ weakly stimulated gastric acid secretion in dogs,[7] and the C-terminal sequence of CCK-PZ and of antral gastrin are alike for at least two and possibly as many as five residues.[28]

The release of gastrin from antral mucosa is under cholinergic control by the parasympathetic postganglionic nerve endings. Release of gastrin by acetylcholine may be initiated by reflexes of the cephalic phase or vagovagal reflexes of the gastric phase. Also, short intramural reflexes, completed within the wall of the stomach and not requiring extrinsic nerves, can cause cholinergic release of gastrin. These local reflexes can be initiated by distending the antrum or by bathing the mucosa with certain chemicals such as ethanol, n-propanol, glycine, β-alanine, and serine.[12] Present evidence indicates that all physiological gastrin release is cholinergic. Acid bathing the antral mucosa inhibits the release of gastrin regardless of what stimulus is acting.

The spectrum of action of gastrin is surprisingly broad. In addition to stimulation of gastric acid secretion, it also weakly stimulates secretion of pepsin, weakly stimulates secretion of pancreatic bicarbonate, strongly stimulates secretion of pancreatic enzymes, and weakly stimulates secretion of biliary bicarbonate. All these actions of gastrin may be regarded as "physiological" in the sense that they can be produced by administration of exogenous gastrin in doses lower than those required for maximal stimulation of gastric acid secretion and in that they can be mimicked by endogenous release of gastrin.[20] Gastrin causes contraction of smooth muscle of most parts of the gastrointestinal tract, including stomach, small intestine, colon, and gallbladder. These motor actions have as yet been demonstrated only with rapid intravenous injection of large doses, so their possible physiological role is not established. Large doses given by rapid intravenous injection also inhibit gastric acid secretion, but this pharmacological action is seen only in the dog.[13]

There are two diseases in which gastrin plays a role. The first is jejunal ulcer occurring in patients who have had a portion of the antrum isolated as a blind pouch attached to the duodenum with a Billroth II reconstruction. The isolated antrum, shielded from the inhibitory effect of being bathed by gastric acid, releases gastrin in an uncontrolled fashion, resulting in hypersecretion and severe jejunal ulceration. Removal of the "noxious remnant" of antrum, without any other surgical alteration, leads to cessation of hypersecretion and healing of the ulcer.[32]

The second disease in which gastrin plays a role is Zollinger-Ellison syndrome.[36] The essential features are (1) one or, more often, multiple adenomas or adenocarcinomas of the islet cells of the pancreas that produce gastrin; (2) high rate of gastric secretion even in the basal state, usually more than 20 mEq. per hour; and (3) severe peptic ulcers, often multiple and sometimes in unusual locations such as the first portion of the jejunum. The disease may occur alone or it may be part of a familial pattern of multiple endocrine adenomas. Other organs commonly involved are parathyroids, adrenals, anterior pituitary, and thyroid. An affected person may have tumors in one, several, or all of these glands. The tumors of some of the endocrine glands overproduce hormones; others may be "silent."

Extracts of Zollinger-Ellison tumors have the same spectrum of biological activity as gastrin. Gastrin isolated from tumors has been shown to be identical in amino acid composition to human antral gastrin.[17]

Antibodies to human synthetic gastrin have been prepared.[33] It has not yet been determined whether these antibodies cross-react with cholecystokinin-pancreozymin, which probably has the same C-terminal sequence as gastrin. When strong and specific antibodies to gastrin are available they should be applicable to a radioimmunoassay that could determine plasma levels of gastrin in health and in various diseases including Zollinger-Ellison syndrone. Fluorescent antibody could help determine which cells make gastrin.

SECRETIN

Hog secretin has 27 amino acid residues: His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2. Like gastrin, its C-terminal residue is an amide. No analogs or fragments of the molecule with secretin-like activity have been found.

The first attempt at synthesis of secretin[3] yielded a material with about one half the potency of natural secretin. When side-products arising from rearrangement of the aspartic acid in position 3 were eliminated[30] the material was found to be equal to natural secretin in potency, about 4 clinical units per microgram.

Secretin is released from the mucosa of the upper small intestine when it is bathed with acid, amino acids, or fatty acids. Hydrogen ion is by far the most potent releaser. Nothing is known about the specificity of other releasers – for example, which amino acids are most effective.

Pure secretin has the following actions: (1) stimulation of pancreatic flow and bicarbonate output;(2) stimulation of biliary flow and bicarbonate output; (3) inhibition of gastrin stimulated gastric acid secretion;

and (4) inhibition of gastric motility. Since synthetic secretin has been shown to have all four of these actions, they may be regarded as properties of secretin itself and not attributable to contaminants. Since all of these actions occur at doses that are well below the maximal dose for pancreatic flow, they may all be regarded as occurring under physiological conditions, a view supported by the fact that all of these effects can be produced by endogenous secretin released when gastric acid is allowed to enter the duodenum. All four actions of secretin counteract duodenal acidification; secretin is nature's antacid.

Inhibition of gastric secretion and motility by secretin are enterogastrone-like actions. Whether secretin is the only "enterogastrone" or just one of a group of substances with such actions is unknown.

There are no diseases known to be associated with production of too little or too much secretin.

Secretin has been used for years as a stimulant of pancreatic secretion in clinical tests used in the diagnosis of pancreatic disease. Now that highly purified material is available that can be given in doses that cause maximal or near maximal rates of pancreatic secretion,[26] perhaps this test will gain wider use. However, the test requires precise placement of a double-lumen tube to allow separate and complete aspiration of gastric and duodenal contents, so the chance for technical error is great.

I have suggested[19] that secretin might be useful in the treatment of duodenal ulcer because it causes alkalinization of the duodenal bulb, both in patients with ordinary duodenal ulcer and in those with Zollinger-Ellison syndrome. We have recently found that secretin is effective in stimulating high rates of pancreatic flow for several hours when injected subcutaneously in dogs; this opens the possibility of developing a depot form of secretin that would have effects lasting many hours.

CHOLECYSTOKININ-PANCREOZYMIN

Two separate hormones were postulated on the basis of physiological studies, but chemical purification showed that the two actions of intestinal mucosal extracts resided in a single molecule with 33 amino acid residues. The hormone has been isolated as a pure polypeptide and the constituent amino acids have been identified,[28] but the full sequence of all the amino acids has not yet been worked out, nor has the structure of the hormone been proved by total synthesis, as has been accomplished for both gastrin and secretin.

Cholecystokinin-pancreozymin (CCK-PZ) has the same C-terminal sequence of amino acids as gastrin for at least two and perhaps as many as five residues.[28] CCK-PZ and gastrin have the same spectrum of biological activities, but the ratio of one activity to another differs markedly. For example, CCK-PZ is a very weak stimulant of gastric acid secretion in comparison with gastrin,[7] and gastrin is a very weak contractor of the gallbladder in comparison with CCK-PZ,[35] but both hormones are strong stimulants of pancreatic enzyme secretion.[31] Depending on dose and method of testing, CCK-PZ has been found under some circumstances to stimulate gastric secretion and motility, under others to inhibit these actions.[4, 7, 11] To what extent these discrepancies are attributable to use of impure hormone containing extraneous substances and to what extent they stem from exceeding the physiological dose range with exogenous hormone, remains to be seen.

Fatty acid, amino acids, and hydrogen ion (listed in order of decreasing potency) release CCK-PZ from upper intestinal mucosa and cause contraction of the gallbladder and stimulation of secretion of pancreatic enzymes. Determination of the possible role of CCK-PZ as an "intestinal gastrin," as one of the "enterogastrones," as a stimulant of smooth muscles other than the gallbladder, and as a mediator of other actions awaits availability of adequate supplies of completely purified hormone.

There are no diseases known to be associated with overproduction or underproduction of CCK-PZ.

CCK-PZ has been used with secretin in diagnostic testing of pancreatic function[5] and in diagnostic cholecystography to empty the gallbladder and visualize the common bile duct with opaque medium expelled from the gallbladder.[10] Neither of these uses has been widely adopted, but with the availability of pure hormone this may change.

REFERENCES

1. Bayliss, W. M., and Starling, E. H.: The mechanism of pancreatic secretion. J. Physiol., 28:325, 1902.
2. Bedi, B. S., Gillespie, G., and Gillespie, I. E.: Effects of a specific gastrin antagonist on gastric acid secretion in pouch dogs. Lancet, *1*:1240, 1967.
3. Bodanszky, M., Ondetti, M. A., Levine, S. D., Narayanan, V. L., von Saltza, M., Sheehan, J. T., Williams, N. J., and Sabo, E. F.: Synthesis of a heptacosapeptide amide with the hormonal activity of secretin. Chemistry & Industry, 42:1757, 1966.
4. Brown, J. C., and Parkes, C. O.: Effect on fundic pouch motor activity of stimulatory and inhibitory fractions separated from pancreozymin. Gastroenterology, 53:731, 1967.
5. Choi, H. J., Goldstein, F., Wirts, C. W., and Menduke, H.: Normal duodenal trypsin values in response to secretin-pancreozymin stimulation with preliminary data in patients with pancreatic disease. Gastroenterology, 53:397, 1967.
6. Code, C. F.: The recognition and assay of gastrone. *In* Shnitka, T. K., Gilbert, J. A. L., and Harrison, R. C., eds.: Gastric Secretion, Mechanisms and Control. London, Pergamon Press, 1967, p. 377.
7. Cooke, A. R.: Effect of pancreozymin preparations on gastric secretion. Nature, *214*:729, 1967.
8. Cooke, A. R.: Comparison of acid and pepsin outputs from gastric fistula dogs in response to histamine, gastrin, and related peptides. Gastroenterology, 53:579, 1967.
9. Cooke, A. R.: The glands of Brunner. *In* Code, C. F., ed.: The Alimentary Canal. Handbook of Physiology, Washington, American Physiological Society, 1967, Volume 2, Section 6, Chapter 61, p. 1087.
10. Edholm, P. R.: Gallbladder evacuation in the normal male induced by cholecystokinin. Acta Radiol. (Stockh.,) 53:257-265, 1960.
11. Edkins, J. S.: On the chemical mechanism of gastric secretion. Proc. Roy. Soc. B., 76:376, 1905.
12. Elwin, C. E., and Uvnäs, B.: Distribution and local release of gastrin. *In* Grossman, M. I., ed.: Gastrin. Berkeley, University of California Press, 1966, p. 69.
13. Emås, S., and Grossman, M. I.: Difference in responses between dogs and cats to large doses of gastrin on gastric secretion. Gut, 8:267, 1967.
14. Gillespie, I. E., and Grossman, M. I.: Inhibitory effect of secretin and cholecystokinin on Heidenhain pouch responses to gastrin extract and histamine. Gut, 5:342, 1964.
15. Gregory, R. A.: Secretory Mechanisms of the Gastro-intestinal Tract. London, Edward Arnold, Ltd., 1962, p. 66.
16. Gregory, R. A.: Enterogastrone – a reappraisal of the problem. *In* Shnitka, T. A., Gilbert, J. A. L., and Harrison, R. C., eds.: Gastric Secretion, Mechanisms and Control. London, Pergamon Press, 1967, p. 469.

17. Gregory, R. A., Grossman, M. I., Tracy, H. J., and Bentley, P. H.: Nature of the gastric secretagogue in Zollinger-Ellison tumours. Lancet, 2:543, 1967.
18. Grossman, M. I.: Gastrointestinal hormones. Physiol. Rev., *30*:33, 1950.
19. Grossman, M. I.: Treatment of duodenal ulcer with secretin: a speculative proposal. Gastroenterology, *50*:912, 1966.
20. Grossman, M. I.: Some aspects of gastric secretion. Gastroenterology, 52:882, 1967.
21. Harper, A. A., and Raper, H. S.: Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. J. Physiol., *102*:115, 1943.
22. Ivy, A. C., and Oldberg, E.: A hormone mechanism for gallbladder contraction and evacuation. Amer. J. Physiol., *86*:599, 1928.
23. Jarrett, R. J., and Cohen, N. M.: Intestinal hormones and plasma-insulin. Lancet, 2:861, 1967.
24. Johnson, D., and Jepson, K.: Use of pentagastrin in a test of gastric acid secretion. Lancet, 2:585, 1967.
25. Kokas, E., and Johnston, C. L., Jr.: Influence of refined villikinin on motility of intestinal villi. Amer. J. Physiol., *208*:1196, 1965.
26. Lagerlöf, H. O., Schütz, H. B., and Holmer, S.: A secretin test with high doses of secretin and correction for incomplete recovery of duodenal juice. Gastroenterology, 52:67, 1967.
27. Morley, J. S., Tracy, H. P., and Gregory, R. A.: Structure-function relationships in the active C-terminal tetrapeptide sequence of gastrin. Nature, 207:1356, 1965.
28. Mutt, V., and Jorpes, J. E.: Isolation of aspartyl-phenylalanine amide from cholecystokinin-pancreozymin. Biochem. Biophys. Res. Comm., *26*:392, 1967.
29. Nasset, E. S.: Secretions in the small intestine. *In* Bard, P., ed.: Medical Physiology. 11th ed. St. Louis, C. V. Mosby Co., 1961, Chapter 25, p. 417.
30. Ondetti, M.: Synthesis of gastrointestinal hormones. *In* International Symposium on the Pharmacology of Hormonal Polypeptides and Proteins. New York, Plenum Publishing Corp., in press.
31. Preshaw, R. M., Adashek, K., Cooke, A. R., and Grossman, M. I.: Failure of Urecholine to potentiate the pancreatic response to exogenous stimuli. Proc. Soc. Exper. Biol. Med., *119*:1040, 1965.
32. Scobie, B. A., McGill, D. B., Priestly, J. T., and Rovelstad, R. A.: Excluded gastric antrum simulating the Zollinger-Ellison syndrome. Gastroenterology, *47*:184, 1964.
33. Stremple, J. F., Abramoff, P., Van Oss, C. J., Wilson, S. D., and Ellison, E. H.: Antibodies to synthetic human gastrin I. Lancet, 2:1180, 1967.
34. Thompson, J. C.: The question of an antral chalone. *In* Grossman, M. I., ed.: Gastrin. Berkeley, University of California Press, 1966, p. 193.
35. Vagne, M., and Grossman, M. I.: Effect of gastrin on motility of gallbladder. Physiologist, *10*:330, 1967.
36. Zollinger, R. M., and Grant, G. N.: Ulcerogenic tumor of the pancreas. J.A.M.A., *190*:181, 1964.

Veterans Administration Center
Los Angeles, California 90073

Clinical Aspects of Gastric Secretion and Gastric Analysis

PAUL H. JORDAN, JR., M.D.*

It is generally believed that peptic ulceration of gastrointestinal mucosa results from the corrosive action of hydrochloric acid. Emotional and physical stress, hypermotility, vascular spasm and thrombosis, infection, allergy, and reduced and altered mucus production are some of the possible factors contributing to increased susceptibility of the mucosa to ulceration. While most of these factors have been excluded from consideration, gastric mucus is known to exert an important protective role in the prevention of peptic ulcer. At present, however, hypersecretion of hydrochloric acid is considered the most important etiological factor in ulcer production, although the mechanism by which this hypersecretion occurs remains unknown.

In 1752, Reaumur,[28] studying his pet buzzard, presented evidence that gastric juice contained acid, which was later identified as hydrochloric acid by Prout.[27] Long before these studies, alkalinizing agents were effectively used to provide symptomatic relief and to heal peptic ulcers. The cause-and-effect relationship between acid gastric juice and peptic ulcer was supported by the work of Claude Bernard and of Dragstedt, showing that unbuffered gastric juice can digest all living tissue, including gastric mucosa.[9] Subsequently, Hay et al.[16] demonstrated that sustained histamine stimulation of gastric acid produced peptic ulcers in dogs which were similar to those occurring in man.

The role of acid in the pathogenesis of peptic ulcer is further suggested by the fact that mean acid secretion is higher for patients with than for those without duodenal ulcer. Unfortunately, the mean rates of acid secretion in these two groups overlap to such an extent as to exclude the rate of secretion in the individual patient as a basis for diagnosis. The degree of overlap suggests that the development of an ulcer is not totally dependent on the quantity of acid produced. That peptic ulcer does not develop in every person who secretes acid is due to its neutralization by gastric mucus, saliva, and ingestion of food. The autoregulating mechanisms within the antrum and duodenum which inhibit acid production when the pH in these areas falls to a critical level are also

---

*Chief of Surgery, Veterans Administration Hospital; Professor of Surgery, Baylor University College of Medicine, Houston, Texas

Medical Clinics of North America—Vol. 52, No. 6, November, 1968

important protective mechanisms. It appears that the development of a peptic ulcer results from disturbance of the balance between protective and aggressive forces acting on the mucosa. Not all of these factors are known. Because of the acid-ulcer relationship and the relative ease with which gastric juice can be collected and the acid measured, this parameter has been exhaustively studied in efforts to establish meaningful criteria for diagnosis, selection of treatment, and prediction of therapeutic results.

TECHNIQUE OF GASTRIC ANALYSIS

Gastric analysis performed by using a stomach tube to sample the gastric contents after a standard meal was introduced by Leube in 1876.[23] Until recently, modifications such as the Ewald carbohydrate test meal were utilized widely and considered superior because they gave information regarding motor as well as secretory function. To avoid subjecting patients to the trauma of swallowing tubes, tubeless methods were developed using cation exchange resins. These methods depended on hydrogen ions releasing quinine[31] or Azure A[32] from the resins, and their ultimate excretion in urine. These techniques are unsatisfactory for quantitative studies, but are useful qualitatively to determine whether or not acid is secreted.

Pavlov[26] demonstrated the relationship between nervous stimulation and parietal cell secretion. Carlson,[28] unlike Pavlov, believed that normal people continued to secrete gastric juice in small amounts during the interdigestive period at night. Subsequently, Henning and Norpoth[17] reported that duodenal ulcer patients, in contrast to normal patients, secreted large amounts of acid during sleep.

As an extension of this work, Dragstedt and co-workers[34] preferred the 12-hour nocturnal gastric secretion test, since they believed that acid secreted under the conditions of this test best reflected the secretory potential of the cephalic phase of gastric secretion, which they considered the key etiological factor in the pathogenesis of duodenal ulcer. Because of the time required for constant surveillance to insure accurate collections, the 12-hour nocturnal secretion test was generally replaced by fractional collection tests done over a one-hour to four-hour period in the early morning with the patient in a fasting condition. The analysis of gastric juice in the shorter collection periods has been shown to supply information comparable to that provided by the longer periods.[10, 24]

The reliability of gastric secretory studies is directly related to the care taken in their execution. All tests should be done with the patient in a fasting state. Medications that might affect the results must be discontinued in advance of the study. The patient must be kept from the sight, smell, or taste of food before and during the test, which should be performed in a quiet, inoffensive environment, with the patient in a reclining position. The nasogastric tube (preferably a double-lumen sump-type tube) should be passed with as little trauma as possible, positioned in the stomach under fluoroscopic control, and connected to a Steadman pump operating at a maximum of five pounds pressure.

The volume and content of the gastric residual is examined first for evidence of gastric retention or bleeding. Thereafter each 15-minute specimen is measured for volume, pH, and total milliequivalents of HCl, by titration with 0.1 N NaOH to pH 7.3. The patient must be constantly supervised to insure continuous suction, to prevent obstruction of the tube, to reposition the tube if necessary, and to observe for any other defects in the system which would invalidate the results.

A major problem with the basal secretory test and all other gastric analyses, particularly when done in patients who have had a previous gastric resection, is the uncertainty regarding the accuracy of collections. To cope with this, techniques were devised using "nonabsorbable" markers such as phenol red or polyethylene glycol. The marker is introduced into the stomach at a constant rate throughout the test; the total amount of gastric secretion produced is determined on the basis of the volume collected and the percentage of marker recovered in the gastric aspirate. Such dilution indicator techniques are cumbersome and are not generally used in clinical studies. In addition, their validity in man is questionable and difficult to evaluate.

Basal gastric secretion studies provide information regarding acid produced under a special circumstance which may have little relevance to what actually occurs in man under daily living conditions. The existence of anacidity cannot be determined by this means, for such a state requires the absence of acid after stimulation with histamine. The overlap in acid production among patients with duodenal ulcer, gastric ulcer, gastric carcinoma, and normal patients is sufficiently great that the test is not useful for diagnostic purposes, nor does it provide information regarding which type of therapy is best utilized in a particular patient.[15] The basal secretory test does provide a reference with which results from other tests can be compared.

HISTAMINE TESTS

Histamine and its analog, betazole hydrochloride (Histalog), have been used extensively in clinical evaluation of gastric secretion. Both drugs are powerful stimulants of gastric secretion, but the results obtained with doses less than that required for maximal stimulation are no more helpful than the basal secretory test.

In 1953 Kay[19] introduced an augmented histamine response (AHR) test in which a sufficiently large dose of histamine (40 μg. per kg.) was given to produce a near-maximal parietal cell response. This test became popular, and in many laboratories Histalog (1.5 to 1.7 mg. per kg.) was substituted to avoid the side reactions of histamine. The maximal response to Histalog is slightly greater than that to histamine and is highly satisfactory for use in the test.[35] Results may be expressed by indicating either (a) the amount of acid secreted between 15 and 45 minutes after injection; (b) the amount secreted for one hour immediately after injection; or (c) the greatest amount secreted for two consecutive 15-minute periods. Kay[20] found an excellent correlation among all three measurements in patients with intact stomachs and in those who had undergone vagotomy. Card[6] showed an equally valid relationship between the AHR and the number of parietal cells. Rune[30] demonstrated that the AHR approximated the secretory response to a meal, thus adding to the significance of the test by showing that the response was within the physiological range.

It was anticipated that this test might aid in diagnosis and in selection of operative or nonoperative treatment best suited for the individual patient. Results in this regard were as disappointing as similar attempts using basal secretory studies.[36] Mean acid secretion in cases of gastric ulcer or gastric cancer is less than in normals, and mean secretion in duodenal ulcer patients is higher than that of any other group. Nevertheless, the range in all groups is so wide that the individual response is of little diagnostic value.

While the test cannot stand alone as a diagnostic tool, it can be helpful in the context of other information. We agree with Kay[20] that an AHR of 20 mEq.HCl in 30 minutes strongly suggests a peptic ulcer in the patient who has symptoms of ulcer, but in whom the roentgenograms are repeatedly negative. The possibility of cancer cannot be excluded by the test, for the response in some patients of this group falls within the normal range. The absence of achlorhydria does not exclude the presence of gastric cancer. However, when a technically satisfactory AHR test demonstrates achlorhydria (defined by Card and Sircus[6] as that state in which the pH of gastric juice does not fall below 6.0 after maximal histamine stimulation), the possibility of peptic ulceration is excluded and malignant disease is indicated if a gastric lesion is seen on the roentgenograms.

Patients with an unusually high gastric secretory rate in the basal stage, and who are suspected of having a Zollinger-Ellison tumor, should have an AHR test. Sixteen of 21 such patients reported by Ellison[13] were secreting at their maximum capacity during the basal state. No further augmentation of secretion occurred with stimulation in these patients.

Histamine achlorhydria was once required for diagnostic confirmation of pernicious anemia. While this indication for gastric analysis is still valid, it has been supplanted by more specific hematological tests for the diagnosis.

PENTAGASTRIN TEST

Gregory[2] and his colleagues, who purified and synthesized gastrin, have demonstrated that the active portion of the molecule is the C-terminal tetrapeptide,[25] which has subsequently been commercially produced as a synthetic pentapeptide called pentagastrin. Pentagastrin was first investigated in the United Kingdom as a substitute for histamine and Histalog in the maximal secretory response test. To avoid inconsistent interpretation of results, several centers cooperated in the study and jointly reported their findings.[1] The maximal secretory response to pentapeptide occurred with a dose of 6 μg. per kg. administered either as a single subcutaneous injection or as the intravenous hourly rate. The response by either route was almost identical to the maximal response obtained with histamine. Reproducibility of the test was good. Approximately 20 per cent of patients experienced mild abdominal discomfort or a sensation of faintness, but in no case were these severe enough to require cessation of the test. Similar results using pentagastrin were reported by others.[22]

Investigators hoped that pentagastrin might represent a stimulus more physiological than histamine, and therefore might provide more useful information regarding diagnosis and treatment. While pentagastrin provides a powerful new tool for the study of gastric physiology, the clinical results thus far do not indicate that this test is superior. The only proven advantage of pentagastrin to date is its lower incidence of side effects.

INSULIN TEST

Since 1943, when Dragstedt and Owens[8] introduced vagotomy for treatment of duodenal ulcer, increased reliance has been placed on this procedure to reduce acid secretion. No longer is extensive resection of the parietal cell mass considered necessary or desirable. Good results associated with limited gastric resections depend mainly on an accompanying vagotomy, for antral resection without vagotomy has long been recognized as inadequate in the treatment of duodenal ulcer. When vagotomy is combined with pyloroplasty or gastroenterostomy, adequate reduction of acid secretion is totally dependent on a satisfactory vagotomy.

What constitutes an adequate vagotomy? To prevent recurrent ulcer, vagotomy may be adequate without being complete, but since it is impossible to predetermine the degree of acid secretion a person can tolerate without risk of recurrent ulceration, the surgeon must strive for complete vagal denervation in all cases. To check for incomplete vagotomy, the insulin test described by Hollander has been widely used. This test is based on the principle that hypoglycemia stimulates the vagal centers. After a basal secretory study, a single intravenous injection of insulin (0.2 μg. per kg.) is given. For a valid test, we require that the blood sugar level fall below 40 mg. per 100 ml. or less than 50 per cent of the fasting level, whichever is lower. Hollander's original criterion for an incomplete vagotomy was a rise in acid concentration either to 20 mEq. per liter above the control level, or to 10 mEq. per liter if the basal secretion was anacid. Alternatives to Hollander's criterion were proposed by Waddell,[34] Ross and Kay,[29] Bachrach,[3] and Bank.[4] The different criteria that have been proposed for a positive response are arbitrary. For this reason we have interpreted any response as representing a potentially unsatisfactory vagotomy. In our opinion, one can be reasonably certain that total vagotomy has been accomplished only when the stomach secretes acid in response to histamine but secretes no acid under basal conditions and after insulin hypoglycemia. We use these criteria because we have seen recurrent ulcer in patients in whom the response to insulin hypoglycemia was within the limits set by Hollander for complete vagotomy.

In spite of problems of interpretation, the Hollander test is useful for confirmation of complete vagotomy. Nevertheless, there are special considerations which must be kept in mind when this test is used. Spontaneous gastric secretion is inhibited for approximately 30 to 45 minutes after injection of insulin. If only a few intact vagal fibers remain after vagotomy, the inhibitory action of insulin may obscure a secretory response which might otherwise be evident.

The incidence of false positive tests is difficult to evaluate because of the controversy over what constitutes a positive test. If the secretory test is clearly positive after operation, it will not subsequently become negative; on the other hand, a false negative may occur if the test is performed too soon after operation, before residual nerve fibers have recovered from the trauma of manipulation. A false negative may also result from failure to avoid the pitfalls that may occur in the performance of any gastric analysis and especially those peculiar to this test. Whether a negative test will become positive because of nerve regeneration is still open to question. Most observers feel that this does not occur, although there is some experimental evidence to suggest that in the dog, vagus fibers responsible for motor function regenerate.[18]

To circumvent the inhibitory effect of insulin, 2-deoxy-D-glucose (2-DG) was studied in animals and man.[11, 12, 21] This drug is a powerful stimulant of gastric secretion if vagal innervation of the parietal cells is intact. 2-DG appears to act by formation of nonmetabolizable 2-DG-6-phosphate, resulting in cytoglucopenia that causes vagal stimulation in basically the same manner as insulin. Since 2-DG does not produce an initial inhibitory effect on gastric secretion, it promises, if proven nontoxic to the liver, to be an excellent agent to test the completeness of vagotomy.

Several reported series of postvagotomy insulin studies using Hollander's criteria for complete vagotomy indicate that incomplete vagotomy may occur in 16 to 30 per cent of patients. His criteria, as well as our own for complete vagotomy, may be too strict for defining an adequate vagotomy, since complete vagotomy may not be essential to cure an ulcer. Ross and Kay[29] reported that a positive insulin response in the first 45 minutes after stimulation indicates incomplete vagotomy, and that such patients are vulnerable to recurrent ulcer. Those with a positive response after 45 minutes probably have vagotomies which are incomplete but adequate to prevent recurrent ulcer. These authors also reported that the augmented histamine response after vagotomy was reduced 67 per cent in patients with negative insulin tests, 9.4 per cent in the early positive group, and 53.2 per cent in the late positive group. Since patients with late insulin responses developed no recurrent ulcers, and the reduction in their AHR was nearly that observed in the group with a negative insulin response, it was suggested that late positive insulin responses indicated incomplete but adequate vagotomies. The interpretation of the insulin test in terms of a combination of factors, rather than any single criterion, may be more meaningful in discerning whether an incomplete vagotomy is adequate clinically.[4, 20]

The ultimate test for an inadequate vagotomy is the recurrence of ulceration. As experience accumulates, it appears that a vagotomy which is inadequate when combined with a drainage procedure may be adequate when combined with a limited distal gastric resection.

MEDICAL VAGOTOMY

In an attempt to determine preoperatively the effect of vagotomy on gastric secretion, Gillespie and Kay[11] compared the consequences of pharmacological blockade and of operative vagectomy on the AHR. Hexamethonium bromide, atropine, Pro-Banthine, and hyoscine bromide were used in various combinations and dosages. The reduction in gastric secretion achieved by vagotomy was frequently underestimated on the basis of the "medical" vagotomy, and predictions in individual cases were sufficiently inaccurate to diminish the usefulness of the test as a means of selecting those patients who would most benefit by vagotomy. Thus far, no type of gastric analysis has withstood the test of time and provided information which allows the selection of the optimum operative or nonoperative therapy for the individual patient with duodenal ulcer.

CONCLUSIONS

The occurrence of peptic ulcer is the result of a shift in the balance of aggressive and defensive factors, permitting hydrochloric acid to digest exposed gastrointestinal mucosa. Undoubtedly, some of these factors are unknown, while others that are identified cannot be measured readily. The majority of gastric analyses that have been used are concerned with measurement of hydrochloric acid produced in the basal state and after different stimuli. This reflects the ease with which hydrochloric acid can be measured and the importance attributed to it in the pathogenesis of peptic ulcer.

Although analysis of acid in gastric contents is a profitable research tool, the clinical usefulness of its measurement has been less rewarding. There is ample evidence that gastric analysis has limited diagnostic value. While the means for basal acid output and maximal histamine response in normal patients are less than in duodenal ulcer patients and greater than in gastric ulcer patients, these values contribute little to the interpretation of results in an individual patient. The overlap in mean rates of acid secretion by normal and peptic ulcer patients emphasizes the probability that factors other than acid exert an important role in the development of this disease.

With few exceptions, measurement of maximal rates of acid secretion is of no critical diagnostic value. The demonstration of achlorhydria excludes the diagnosis of peptic ulcer and supports a diagnosis of pernicious anemia, which does not occur in the absence of achlorhydria. Finally, the augmented histamine response test is helpful in the diagnosis of the Zollinger-Ellison syndrome, since acid produced in the basal state is usually in excess of 10 mEq. per hour and, in many of these patients, is not significantly increased by histamine.

Thus far it has been impossible to select the operation best suited for the individual ulcer patient by means of any form of gastric analysis. The insulin test designed to evaluate completeness of vagotomy is perhaps the most useful gastric analysis, but its interpretation remains a subject of controversy. If Hollander's original criteria are complied with, the test can reliably detect incomplete vagotomy in most instances. The insulin test does not permit us to answer the more important question: What degree of denervation of the stomach is adequate to prevent recurrent ulceration? Even if this question were answered, there is yet no method for performing gastric vagotomy of precisely different gradations.

As a stimulant for gastric secretion, synthetic pentagastrin may replace histamine and Histalog because of its close relationship to natural gastrin. To date there is no evidence to suggest that tests using pentagastrin are superior.

REFERENCES

1. Abernethy, R. J., Gillespie, I. E., Lowrie, J. H., Forrest, A. P. M., Payne, R. A., Barabas, A., Johnston, I. D. A., Burns, G. P., Hobbs, K. E. F., Clegg, R. T., Duthie, H. L., and Fitzgerald, J. D.: Pentagastrin as a stimulant of maximal gastric response in man. A multicentre pilot study. Lancet, *1*:291, 1967.
2. Anderson, J. C., Barton, M. A., Gregory, R. A., Hardy, P. M., Kenner, G. W., MacLeod, J. K., Preston, J., Sheppard, R. C., and Morley, J. S.: The antral hormone gastrin: synthesis of gastrin. Nature, *204*:933, 1964.
3. Bachrach, W. H.: Laboratory criteria for the completeness of vagotomy. Am. J. Digest. Dis., *7*:1071, 1962.
4. Bank, S., Marks, I. N., and Louw, J. H.: Histamine and insulin stimulated gastric acid secretion after selective truncal vagotomy. Gut, *8*:36, 1967.
5. Card, W. I., and Marks, I. N.: The relationship between the acid output of the stomach following "maximal" histamine stimulation and the parietal cell mass. Clin. Sci., *19*:147, 1960.
6. Card, W. I., and Sircus, W.: Anacidity. *In* Jones, S. A., ed.: Modern Trends in Gastroenterology. 2nd series. New York, Paul B. Hoeber, Inc., 1958, p. 177.
7. Carlson, A. J.: The secretion of gastric juice in health and disease. Physiol. Rev., *3*:1, 1923.
8. Dragstedt, L. R., and Owens, F. M. J.: Supradiaphragmatic section of vagus nerves in treatment of duodenal ulcer. Proc. Soc. Exp. Biol. & Med., *53*:152, 1943.
9. Dragstedt, L. R., and Vaughn, A. M.: Gastric ulcer studies. Arch. Surg., *8*:791, 1924.
10. Dragstedt, L. R. II, and Lawson, L. J.: Measurement of fasting gastric secretion. Arch. Surg., *88*:287, 1964.
11. Duke, W. W., Hirschowitz, B. I., and Sachs, G.: Vagal stimulation of gastric secretion in man by 2-deoxy-D-glucose. Lancet, *2*:871, 1965.
12. Eisenberg, M. M., Emås, G. S., and Grossman, M. I.: Comparison of the effect of 2-deoxy-D-glucose and insulin on gastric secretion in dogs. Surg., *60*:111, 1966.
13. Ellison, E. H., and Wilson, S. D.: The Zollinger-Ellison syndrome: Re-appraisal and evaluation of 260 registered cases. Ann. Surg., *160*:512, 1964.
14. Gillespie, I. E., and Kay, A. W.: Effect of medical and surgical vagotomy on the augmented histamine test in man. Brit. Med. J., *1*:1557, 1961.
15. Grossman, M. I., Kirsner, J. B., and Gillespie, I. E.: Basal and Histalog-stimulated gastric secretion in control subjects and in patients with peptic ulcer or gastric cancer. Gastroent., *45*:14, 1963.
16. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Experimental production of gastric and duodenal ulcers in laboratory animals by intramuscular injection of histamine in beeswax. Surg. Gynec. Obst., *75*:170, 1942.
17. Henning, N., and Norpoth, L.: Die Magensekretion wåhrend des Schlafes. Deutsches Arch. f. klin. Med., *172*:558, 1932.
18. Jefferson, N. C., Geisel, A., Lott, P., and Necheles, H.: Vagus regeneration in dogs. Surg., *61*:808, 1967.
19. Kay, Andrew: Effect of large doses of histamine on gastric secretion of HCl; augmented histamine test. Brit. Med. J., *2*:77, 1953.
20. Kay, Andrew: Memorial lecture: an evaluation of gastric acid secretion tests. Gastroent., *53*:834, 1967.
21. Konturek, S. J.: Effect of insulin and 2-deoxy-D-glucose on HCl secretion from the normal and vagally denervated stomach. Acta. Med. Pol., *8*:195, 1967.
22. Konturek, S. J., and Lankosz, J.: Pentapeptide infusion test. Scand. J. Gastro., *2*:112, 1967.
23. Leube, W. O.: Bemerkungen über die Abösung der Magenschleimhaut durch die Magensonde und ihre Folgen. Deutsches Arch. f. klin. Med., *18*:496, 1876.
24. Levin, E., Kirsner, J. B., and Palmer, W. L.: A simple measure of gastric secretion in man: comparison of one-hour basal secretion, histamine secretion and twelve-hour noctural gastric secretion. Gastroent., *19*:88, 1951.
25. Morley, J. S., Tracy, H. J., and Gregory, R. A.: Structure-function relationships in the active C-terminal tetrapeptide sequence of gastrin. Nature, *207*:1356, 1965.
26. Pavlov, I. P.: The Work of the Digestive Glands. Trans. by W. H. Thompson. 2nd ed. London, Charles Griffin & Co., 1910, p. 53.

27. Prout, William: On the nature of acid and saline matters usually existing in the stomach of animals. Trans. Royal Soc. London, *114*:45, 1824.
28. Reaumur, R. A. F.: Sur la digestion des oiseaux. Hist. Acad. Roy. Sci., p. 266, 1756.
29. Ross, B., and Kay, A. W.: The insulin test after vagotomy. Gastroent., *46*:379, 1964.
30. Rune, S. J.: Comparison of the rates of gastric acid secretion in man after ingestion of food and after maximal stimulation with histamine. Gut, 7:344, 1966.
31. Segal, H. L., Miller, L. L., and Morton, J. J.: Determination of gastric acidity without intubation by use of cation exchange indicator compounds. Proc. Soc. Exp. Biol. Med., *74*:218, 1950.
32. Segal, H. L., Miller, L. L., and Plumb, E.: Tubeless gastric analysis with an azure A ion-exchange compound. Gastroent., *28*:402, 1955.
33. Thornton, F. T., Jr., Storer, E. H., and Dragstedt, L. R.: Supradiaphragmatic section of the vagus nerves. J.A.M.A., *130*:764, 1946.
34. Waddell, W. R.: The acid secretory response to histamine and insulin hypoglycemia after various operations of the stomach. Surg., *42*:652, 1957.
35. Ward, S. V., Gillespie, I. E., Passaro, E. P., and Grossman, M. I.: Comparison of Histalog and histamine as stimulants for maximal gastric secretion in human subjects and in dogs. Gastroent., *44*:620, 1963.
36. Wormsley, K. G., and Grossman, M. I.: Maximal Histalog test in control subjects and patients with peptic ulcer. Gut., 6:427, 1965.

Baylor University College of Medicine
1200 Moursund
Houston, Texas 77031

Cytological Examination in Gastrointestinal Tract Disease

LLOYD L. BRANDBORG, M.D.*

JULIUS WENGER, M.D.**

In spite of a rather voluminous literature documenting the accuracy of exfoliative cytology for cancer diagnosis in the gastrointestinal tract, the method is not widely accepted. Many factors have been responsible; not the least is the scarcity of skilled cytotechnicians. The accepted role of roentgenological and endoscopic methods as the final "authority" have also contributed. In specialized laboratories employing skilled cell collection, rapid processing, precise interpretation, etc., exfoliative cytology approaches histological diagnosis in cancer.

Successful gastrointestinal cytology requires fulfillment of several important conditions. They include a clean organ, a well-hydrated patient, skilled cell collection and processing, expert interpretation, and accurate reporting.

TECHNIQUES

No ideal cell collection technique is available at any level of the gut. Lavage methods yield the best accuracy, are little discomforting to the patient, and may be performed by cytotechnologists. In the stomach, chymotrypsin lavage has resulted in the highest reported accuracy,[1] yielding the best specimen for interpretation,[2] and is simple to perform. Lavage with saline or Ringer's solution has yielded good, but lower, accuracy.[7] Most abrasive techniques, such as balloons and brushes, require a physician in attendance, may be discomforting to the patient, decrease accuracy, are potentially dangerous, and should be condemned. Casual cell collection by house officers or untrained personnel, routine submission of the fasting gastric contents to the pathology laboratory for

---

*Chief, Gastroenterology, Veterans Administration Hospital; Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

**Chief, Gastroenterology, and Assistant Chief, Medical Service, Veterans Administration Hospital; Associate Professor of Medicine (Gastroenterology), Emory University School of Medicine, Atlanta, Georgia

"cytology" and cursory scanning of slides provide virtually valueless results. They should be avoided. Superior results are obtained when trained cytotechnologists collect the specimen and are responsible for the scanning and interpretation, the final diagnosis being made by a skilled and interested clinician or pathologist. Cell collection techniques will not be described since they are adequately reported elsewhere.[2, 4, 8, 9]

The gastrointestinal cytology laboratory at the Veterans Administration Hospital, San Francisco, was established in September 1962. Two cytotechnologists share the responsibility for cell collection, fixation, staining, screening, and quality control. The final diagnosis is the responsibility of Dr. Brandborg. The data presented in the tables includes all patients examined from September 1962 through September 1967 (60 months).

The cytologic laboratory at the Veterans Administration Hospital, Atlanta, is an integral part of the clinical laboratory and is supervised by its Chief, Dr. Joseph Mendeloff, Professor of Pathology, Emory University School of Medicine. The laboratory is a general cytology laboratory, offering its services to all divisions of the hospital. Shortage of cytotechnologists made it incumbent upon the gastroenterology service to collect gastrointestinal specimens. (An occasional esophageal specimen was submitted for cytology by the Surgical Service; the specimen was obtained by irrigation at esophagoscopy. We do not recommend this procedure.) The specimens were prepared and screened by expert cytotechnologists. The data presented in the tables span the period from January 1, 1963, to December 31, 1967. The final diagnosis was the responsibility of the Chief of the Laboratory Service or his designate. The Atlanta experience documents that good clinical pathology laboratories can obtain high accuracy in gastrointestinal cytology. Data of this sort are obtainable by any good pathology service, provided the same attention to detail and skill are applied.

Diagnoses are made on the basis of smears prepared from the centrifuged sediment. A "button" is not made for histological examination. The preparation of a "button" adds labor, time, and complexity to the procedure. We have never made a diagnosis of cancer in a "button" when diagnostic cells were not present on the smears. The reverse was frequently true prior to abandonment of the "button" which at best provided a pseudo-architecture.

The preferred stain is a modification of Papanicolaou's technique described by Rubin and Benditt.[10] Only one slide from each pair need be scanned. Malignant cells rarely occur on only one slide prepared by smearing the sediment between pairs of slides. The Atlanta VA Hospital employs lavage with 0.15 M acetate buffer at pH 6.0. At the San Francisco VA Hospital chymotrypsin lavage is the method employed for gastric cytological study.

CYTOLOGICAL CRITERIA

The diagnosis of malignant or benign disease is made from the morphology of the *nucleus*. Criteria for malignant disease include irregular abnormal chromatin distribution, hyperchromatism, excessive variation in nuclear size, increased nucleus to cytoplasm ratio, enlarged and multiple nucleoli, thickened nuclear borders, "empty spaces" in nuclei and "potato" nuclei (budding and "pseudopod" formation). The cytoplasmic features aid in differentiation of squamous cell carcinoma from adenocarcinoma. Sparse basophilic cytoplasm with vacuolization and mucous inclusions suggest adenocarcinoma (Fig. 1); orangophilic staining, malignant pearls (Fig. 2), tadpole cells, or fiber cells indicate a squamous origin. Malignant lymphoma cells (Fig. 3) tend to be individually distributed throughout the slide and are not ordinarily seen in sheets or clumps. One malignant cell type predominates (Fig. 3), with occasional forms ranging from primitive stem cells to benign-appearing lymphocytes. In some patients, the predominent cell may appear benign with small numbers of malignant cells. The malignant lymphoma cell is only slightly larger than the normal gastric cell and is easily missed when scanning with only a low-power objective lens (100×). The *nuclear* criteria of malignant disease are present in spite of the small size. The diagnosis should be suspected when substantial numbers of "inflammatory" cells are present on the slide. The presence of Reed-Sternberg cells[6] (Fig. 4) is conclusively diagnostic evidence of Hodgkin's disease of the stomach. The scanner should frequently switch to the high dry objective (400×) to minimize reader error in overlooking malignant lymphoma.

Alterations in benign cells may be confused with malignant disease.[3] Usually they include increased chromatin in nuclei or proportionate increase in both the nucleus and the cytoplasm. Although the chromatin may be "changed," the background chromatin is homogeneously distrib-

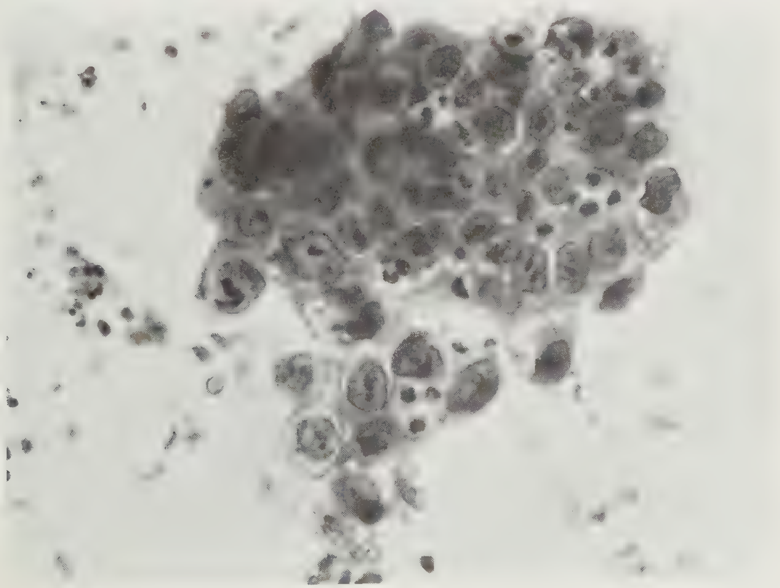

Figure 1. Adenocarcinoma. ×400.

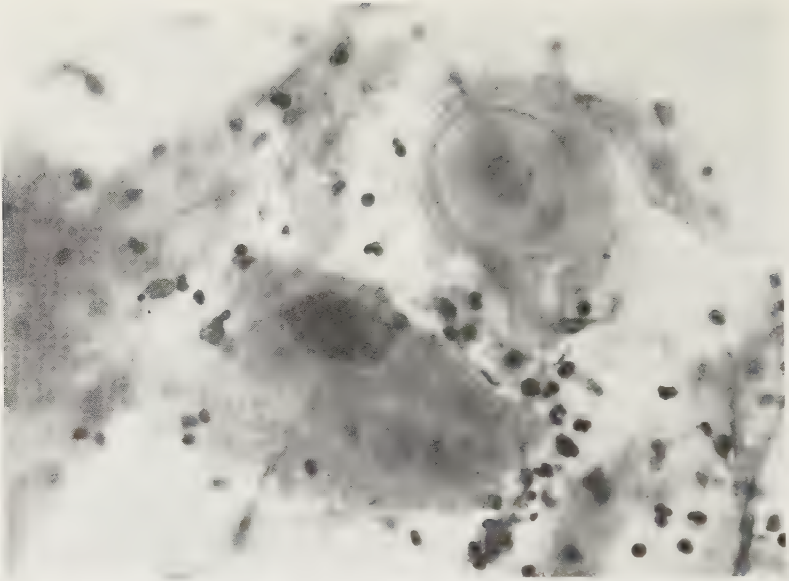

Figure 2. Squamous carcinoma. Malignant pearl is present. Benign cells near it are slightly out of focus. × 400.

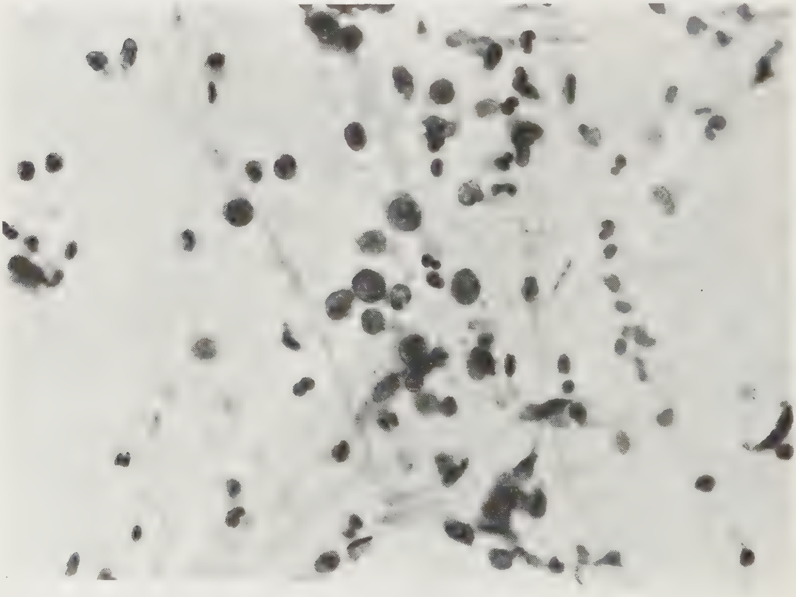

Figure 3. Malignant lymphoma (reticulum cell sarcoma) identified by fine vacuolated cytoplasm. Lymphosarcoma is similar, but smaller. × 400.

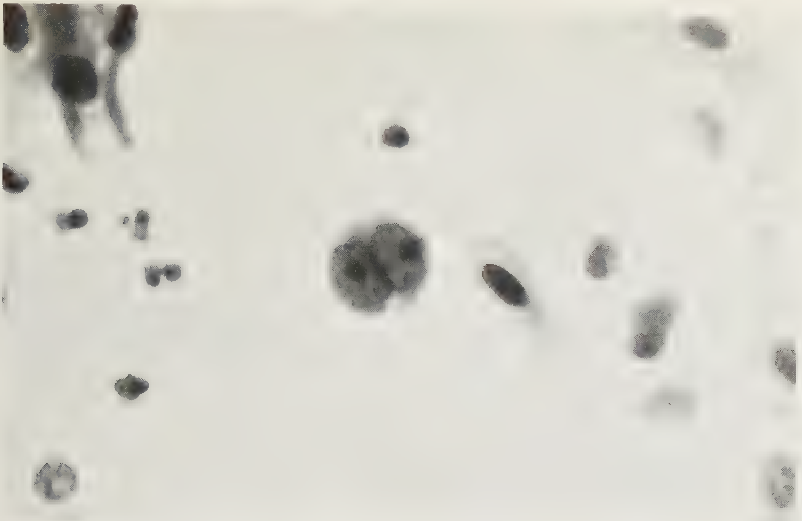

Figure 4. Reed-Sternberg cells as seen in gastric washings from a patient with Hodgkin's disease. × 580.

uted. The changes are seen in inflammatory lesions of the gut, vitamin B_{12} deficiency (untreated pernicious anemia) or folic acid deficiency, folic acid antagonist therapy, megaloblastic anemia of pregnancy, etc. Some elderly patients have large benign cells which may be the result of ill-defined nutritional abnormalities or perhaps senescence. Fibroblasts aspirated from denuded areas may resemble carcinoma in cytologic preparations. Patients should be re-examined after treatment of the specific deficiencies, since the cellular alterations are reversible. However, large gastric columnar cells may be regularly recovered from patients with gastric atrophy.

Patients with viral upper respiratory infections may swallow mononuclear cells which are virtually indistinguishable from those of malignant lymphoma. The diagnosis of malignant lymphoma should not be made in patients with "colds" until the patient has recovered.

ESOPHAGUS

The esophagus is easily examined. The test is indicated in *any patient with dysphagia*, stricture, "esophagitis" abnormalities on roentgenologic examination, and in examination for suspected recurrence of malignant disease. Patients with caustic strictures and achalasia should be studied frequently because of the predisposition to neoplastic change. A simple lavage method[4] has produced the best reported data.

Cytologic Interpretation

Esophageal specimens invariably contain cells from lung, nose, pharynx, and, in compete collections, columnar cells from the gastric fundus. Malignant disease of the esophagus is usually squamous car-

Table 1. *Esophageal Cytology Reports*

HOSPITAL		PATIENTS	NO. BENIGN	NO. MALIGNANT	PER CENT CORRECT
VAH San Francisco	Proved benign	63	61	2*	96.8
	Proved malignant	29	0	29	100.0
VAH Atlanta	Proved benign	36	36	0	100.0
	Proved malignant	19	2	17	89.5

*The esophagus of one of these patients was lined with pylorocardiac columnar epithelium. The "malignant" cells were the nuclei, stripped of their cytoplasm. The other patient had severe alcoholism with both iron and folic acid deficiency. Both patients are alive after 5 years without surgery because we were able to correct the diagnoses. The first report must therefore be classified as false positive.

cinoma (Fig. 2) and resembles that seen originating in other sites. Adenocarcinomas of the esophagus usually originate in the stomach. Primary malignant lymphoma is extremely rare.

Accuracy

Accuracy in the esophagus is the highest of any level of the gut – 94 to 98 per cent[4] (see Table 1). False diagnoses of malignant disease are rare in experienced laboratories.

Case Report

A 68-year-old white male was admitted with 2 months of progressive painless dysphagia. During this time he had lost 50 pounds. The pertinent past history included cirrhosis, diagnosed in 1950, and syphilis in 1921, which was treated first with mercury and later with penicillin.

The physical examination revealed a malnourished cachectic male with a hard nodular liver palpable 7 cm. below the right costal margin and an enlarged spleen felt 5 cm. below the left costal margin. An esophagram shortly after admission demonstrated complete obstruction to barium of the distal esophagus. Its nature was uncertain, the differential diagnosis laying between peptic esophagitis and malignant disease (Fig. 5). Esophagoscopy demonstrated a smooth stricture and esophageal varices. Biopsy was negative. Cytologic examination produced an undifferentiated squamous cell carcinoma. The patient was treated with radiation therapy because of his cirrhosis. There was transient improvement in his swallowing. However, prior to completion of the irradiation, aspiration resulted in a septic lung abscess with bronchial pneumonia from which he expired. At autopsy squamous carcinoma of the esophagus was confirmed.

Comment: Although the outcome in this patient was not satisfactory, the correct diagnosis by cytology permitted selection of appropriate therapy.

STOMACH

The major role of cytology of the stomach is in providing a precise diagnosis of lesions discovered upon roentgenologic or gastroscopic examination, or suspected clinically. Cytological screening of asymptomatic patients for cancer has not proved feasible.[5] Certain "high-risk" patients should, ideally, be examined at regular intervals. These include patients with pernicious anemia, gastric atrophy and achlorhydria, gastric polyps, and Menetrier's disease. Cytology complements other diagnostic techniques and should be used in conjunction with them. The greatest contribution is in areas where x-ray and endoscopy are most difficult. These include lesions of the cardia and fundus. It is of value in the differential diagnosis of ulcerating lesions, large gastric folds and the narrow antrum.

Cytologic Findings

Most of the cells recovered from the stomach originate from other sites, such as the mouth, nose, pharynx, esophagus, and lung. Patients with achlorhydria frequently have bacteria and fungi and occasionally Giardia lamblia. These findings are not indicative of cancer. Variable numbers of lymphocytes, plasma cells, and polymorphonuclear leukocytes are present. Adenocarcinoma is the most common type of gastric malignant disease (Fig. 1). Adenocarcinoma cells are often seen in crowded clumps overlapping one another with indistinct or absent cellular borders. They frequently appear syncytial. The cytoplasmic features of vacuolization, basophilia, etc., help establish their nature. Exfoliative cytology is the only reliable technique of diagnosing malignant lymphoma of the stomach prior to surgery.

Accuracy

The accuracy of cytology in gastric malignant disease in specialized laboratories is on the order of 85 to 95 per cent[1, 7] (Table 2). False diagnoses of cancer are infrequent and do not usually exceed 2 per cent. Accuracy is enhanced if it be required that a diagnosis of either benign or

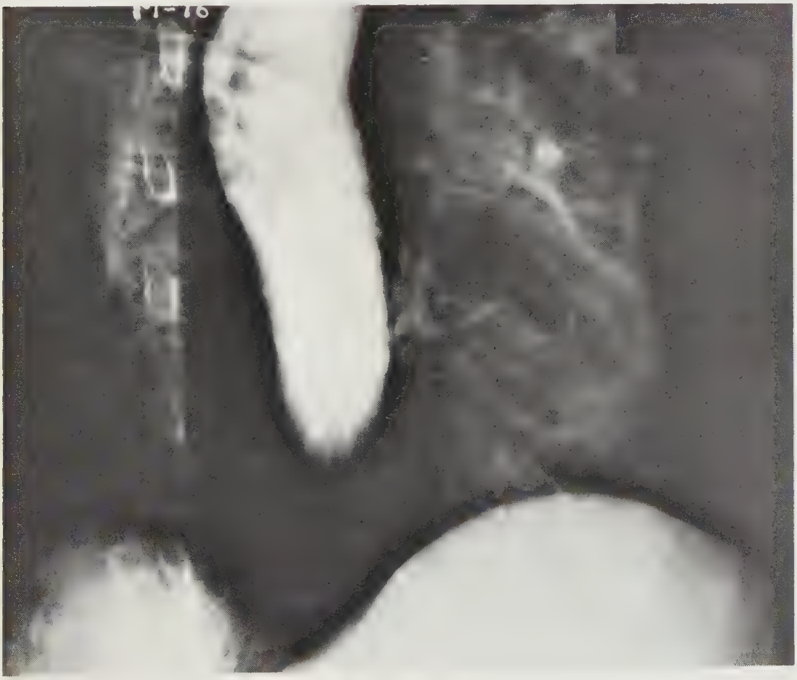

Figure 5. Esophagram demonstrating a dilated esophagus and total obstruction.

Table 2. *Gastric Cytology Reports*

HOSPITAL		PATIENTS	NO. BENIGN	NO. MALIGNANT	PER CENT CORRECT
VAH San Francisco	Proved benign	371	370	1*	99.7
	Proved malignant	70	2	68	97.1
VAH Atlanta	Proved benign	98	95	3†	96.9
	Proved malignant	27	1‡	26	96.3

*"Malignant lymphoma" by cytology. "Lymphoid hyperplasia" by pathology.

†One of these three patients refused surgery and has no evidence of cancer one year later; hence this is considered a false positive test. The second patient had a benign gastric ulcer, and the third had "chronic gastritis." All three patients are alive and well.

‡This patient refused surgery for a nonhealing gastric ulcer and returned two years later with an ulcerating adenocarcinoma at the same site. It is considered a false negative test.

malignant change be made.[6] Misinterpretations of unusual *benign* cells reflect insecurity with cytological interpretation, serve only to confuse the clinician caring for the patient, and frequently result in unnecessary surgery.

Case Report

A 67-year-old white male patient with a three-year to four-year history of ulcer symptoms was admitted on May 19 to the VA Hospital in Atlanta with a hematocrit of 19 per cent and hemoglobin of 7.0 gm. per 100 ml. Physical findings were

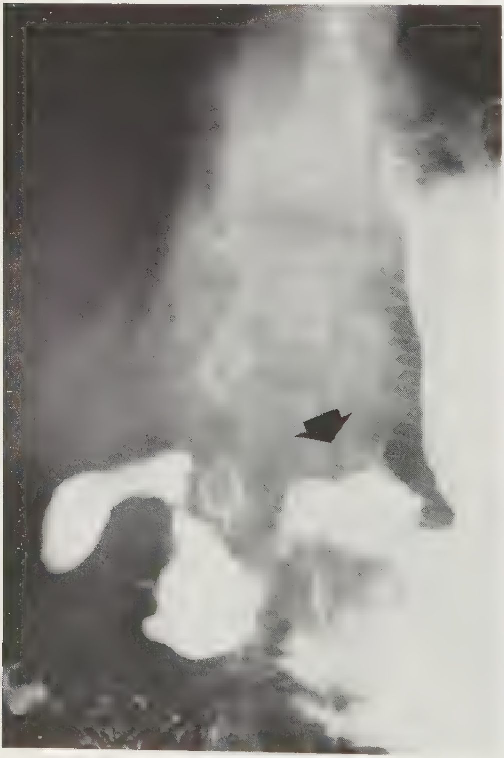

Figure 6. Initial gastric roentgenogram showing large lesser curvature gastric ulcer at the angulus. It was presumed to be benign by all roentgenologic criteria.

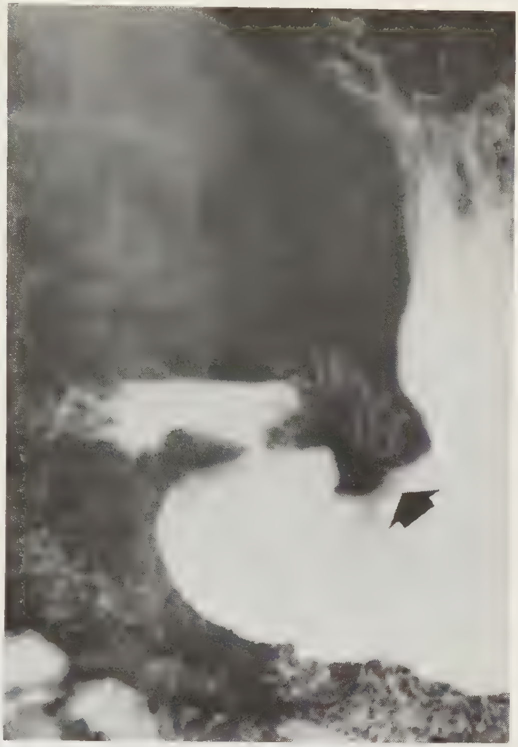

Figure 7. Follow-up roentgenogram made 6 weeks after the first study. The patient was free of symptoms, and there is a small dimple visible at the site of the previously noted large gastric ulcer. The roentgenologist reported almost complete healing of the ulcer crater.

not remarkable. A barium study of the stomach revealed a large ulcer of the lesser curvature (Fig. 6), which responded well to medical therapy. Six weeks later (Fig. 7) the ulcer was almost entirely healed. In spite of the positive cytologic report for adenocarcinoma, the patient felt well, and refused surgery until August 4, when a repeat study showed a small recurrence of the gastric ulcer. At the time of surgery a 4.0 cm. ulcerative carcinoma of the lesser curvature was resected, and only one lymph node on the greater curvature of the stomach revealed neoplastic cells.

Unfortunately, the patient died of viral pneumonia 10 days postoperatively, but no other evidence of cancer was found at postmortem examination.

DUODENAL DRAINAGE

Diagnosis of malignant disease of the pancreas, biliary tract, liver, duodenum, etc., is most difficult[8, 12] with frequently unreliable results. Cytology may detect a malignant process, but negative results are valueless. The highest reported positive accuracy in patients with proven carcinoma from areas draining into the duodenum has been on the order of 55 per cent.[8]

Fluoroscopic control of duodenal intubation is essential. The test is combined with the secretin test for pancreatic function.[12] The specimens are processed in the same way as gastric and esophageal specimens. Cellular components are separated by centrifugation and the secretions analyzed chemically. Prior to the withdrawal of the tube, a three-minute lavage of the duodenum with Ringer's solution is performed and this specimen is also processed.

Cytologic Findings

The duodenal specimen contains scanty numbers of cells. Cells from the upper gastrointestinal tract, lung, etc., are usually present. Small bowel epithelium may be recognized by the smaller size, smaller nucleus, and more homogeneous chromatin distribution. Brush borders are present. Malignant cells resemble those originating elsewhere and are largely adenocarcinoma. The site of origin cannot be predicted from their appearance. The malignant cells may be scanty and partially digested. However, primary malignant disease of the duodenum is readily accessible to cytological diagnosis.

Accuracy

Accuracy is low even after maximal effort to obtain the specimens. The indications for duodenal cytology are difficult to define. Exfoliation of cells suitable for diagnosis does not occur often in the patient with total, malignant biliary obstruction. It would be desirable to examine these patients before they become jaundiced. Extrahepatic biliary obstruction almost invariably requires surgical therapy regardless of cytological findings. Unfortunately, there are no reliable methods of "early" diagnosis of cancer in this area.

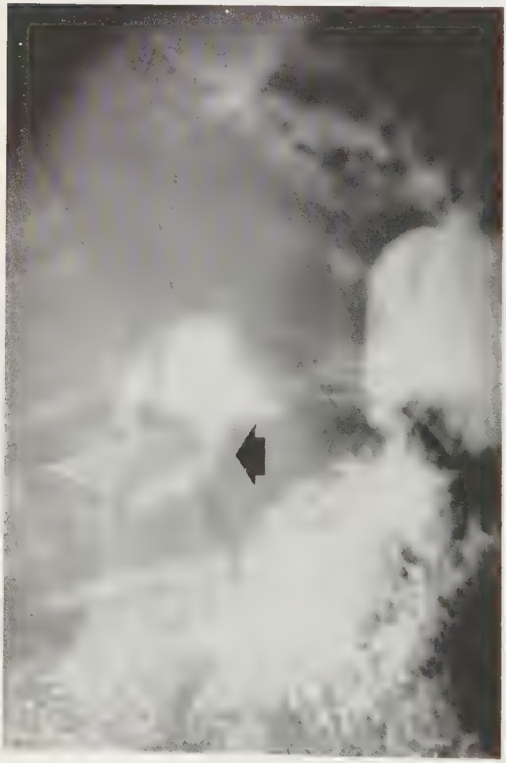

Figure 8. A portion of the upper gastrointestinal roentgenogram (lateral view) showing polypoid filling defects of the second and third portion of the duodenum.

Case Report

A 45-year-old white man was admitted to the Atlanta VA Hospital with an ill-defined polypoid mass of the duodenum seen at x-ray examination. He had complained of intermittent burning epigastric pain for 1½ years. X-ray studies (Fig. 8) confirmed the polypoid mass seen in the second and third portion of the duodenum. Duodenal intubation revealed adenocarcinoma cells, and there was a normal pancreatic response to the secretin test. A radical resection of the duodenum was accomplished and the patient survived for 5 years, at which time a final illness was characterized by multiple cerebral thromboses of the basilar-vertebral arteries. At postmortem examination there was no evidence of carcinoma.

COLON

Most carcinomas of the colon occur within the reach of the sigmoidoscope and are accessible to biopsy. These lesions do not require cytological examination. An exception is villous adenoma, which may be misdiagnosed as benign, even with multiple biopsy specimens. Villous adenoma should be excised surgically upon discovery. A correct preoperative diagnosis is of value in planning the surgical procedure.

Cytological examination is useful in areas beyond the reach of the sigmoidoscope. It helps in the differential diagnosis of polypoid lesions, in an area of stricture which might be carcinoma or diverticulitis, and occasionally in patients with unexplained iron-deficiency anemia. It would seem desirable to examine patients with ulcerative colitis periodically.

The silicone foam enema[11] may be used for collection of cells and recording a direct impression of lesions. It is applicable only to more distal colon examination but has proved useful in selected patients. The cells adhering to the silicone foam cast are washed off and studied by cytologic methods.

Cytologic Findings

Most colon carcinomas are adenocarcinoma. Malignant changes are somewhat more subtle than those seen in gastric carcinoma. Fecal contamination and substances such as cellulose may partially destroy or obscure the cells during processing and scanning. Diagnostic cells are frequently scarce and poorly preserved. Some cytologic features such as "fronds" suggest the possibility of adenomatous polyps.

Accuracy

Accuracy is on the order of 85 per cent in the colon proximal to the range of the sigmoidoscope. Although cytologic differentiation between benign polypoid lesions and low-grade malignant lesions is extremely difficult, this also applies to tissue sections. False positive diagnoses of cancer are rare and occur most often in direct aspiration from diffuse inflammatory disease such as ulcerative colitis.

Case Report

A 77-year-old man was admitted to the San Francisco VA Hospital with a history of intermittent, bright red blood per rectum which he had observed for approximately 8 months. He had no other associated symptoms nor any weight loss. The pertinent physical finding was an enlarged right lobe of the liver of normal consistency and with a sharp edge. Sigmoidoscopy on several occasions did not demonstrate any lesions. The instrument could not be advanced beyond 15 cm. Barium enemas demonstrated a filling defect in the rectosigmoid region. The report stated that this "could be postinflammatory or carcinomatous narrowing, with the latter less likely." A silicone foam enema recovered adenocarcinoma cells and recorded an impression of an annular adenocarcinoma. The results of a subsequent barium enema examination were interpreted as carcinoma. At surgery, metastases were found and only a palliative resection was possible. The patient was asymptomatic for 6 months, when he expired from an acute myocardial infarction. Approximately 5 days prior to death, he developed sudden onset of jaundice and ascites.

Comment. At a prior admission to the hospital, this patient had been extensively evaluated, and no cause for his rectal bleeding was found. The silicone foam enema for the first time documented the nature of his disease. Although he had only a palliative resection, he was subjectively well until a few days prior to death from a myocardial infarction.

DISCUSSION

Gastrointestinal cytology is accurate and practical. Many factors have prevented its optimal application. One is the scarcity of specially trained cytotechnologists. Unsatisfactory results are to be expected if cell collection technique is casual, if abrasive instruments are used and if scanning of specimens is cursory. If clinicians and pathologists are disinterested, poor results will ensue. Diagnoses such as "atypical," "highly atypical," "Class III," "suspicious," "doubtful," etc., cast doubt on diagnostic accuracy and should be abandoned. The conditions usually associated with unusual benign cells are described under cytologic criteria. Many pathologists are insecure in cytological diagnosis because "invasion" cannot be seen. With strict attention to morphologic criteria, the diagnosis of malignant or benign changes can be arrived at in almost every instance from cytologic smears. Benign disease of the gut cannot be *specifically* (histologically) diagnosed by cytologic methods.

Exfoliative cytology is not intended to supplant roentgenologic or endoscopic examination. The latter two methods are very useful in the study of *in vivo gross pathology.* The application of all available diagnostic techniques will benefit patients.

Expertly performed, exfoliative cytology has proved to be the most accurate technique for diagnosing and excluding malignant disease in vivo, particularly of the esophagus and stomach. It is a sensitive method approaching the accuracy of microscopic pathology. Some tumors are not accessible to cytological diagnosis. Tumors which do not penetrate the mucosa, scirrhous carcinoma (linitis plastica), and far advanced ulcerative carcinoma may not exfoliate malignant cells. Occasionally, gastric cancer will resemble a benign ulcer in all respects except that these lesions usually do not heal.[6] Since it is mandatory that gastric ulcers heal completely by x-ray criteria in order to be called benign, those which do not heal should have subsequent cytologic examination. Giant follicular lymphoma of the stomach exfoliates benign-appearing lymphocytes and this diagnosis is made on tissue sections. Cancers of the stomach which are missed by cytologic methods are ordinarily diagnosed by roentgenology or endoscopy. Exfoliative cytology in overt cancer will reinforce a pathologic diagnosis and give a high degree of confidence. This information may cause the surgeon to alter his operative plan. For example, if gastric lymphoma is present, he may resect tumor which otherwise would be considered inoperable, the patient subsequently being treated by irradiation therapy.

Most patients require only one examination. Approximately 10 per cent of patients will require a repeat examination because of an inadequate sample – for example, lack of benign gastric surface columnar cells (Fig. 9) in the stomach – or because of obscuring barium, food, and other debris. The presence of normal epithelial cells from the site under examination is indication of an adequate cell collection. Malignant cells are less cohesive than normal cells and tend to exfoliate more readily. Rarely esophageal cancer may be missed because of failure to pass the aspirating tube beyond the strictured area.[4]

The above results have been obtained by utilizing morphologic interpretation. Fluorescent staining of exfoliated cells by acridine orange or tetracycline have produced unacceptably high false results and cannot be recommended. Furthermore, fluorescent tests require morphological confirmation.

In practice the patient and his family are most benefited by establishing the *benign* nature of a lesion thought to be malignant by other diagnostic procedures. In patients with a gastric ulcer or an indefinite gastric lesion regardless of their roentgenologic or gastroscopic appearance, a benign cytologic report from a skilled laboratory should result in a decision for medical treatment. If no other *clinical* indications are present, a short period (3 to 4 weeks) of observation is warranted. This short delay probably will not affect the ultimate prognosis. Since the

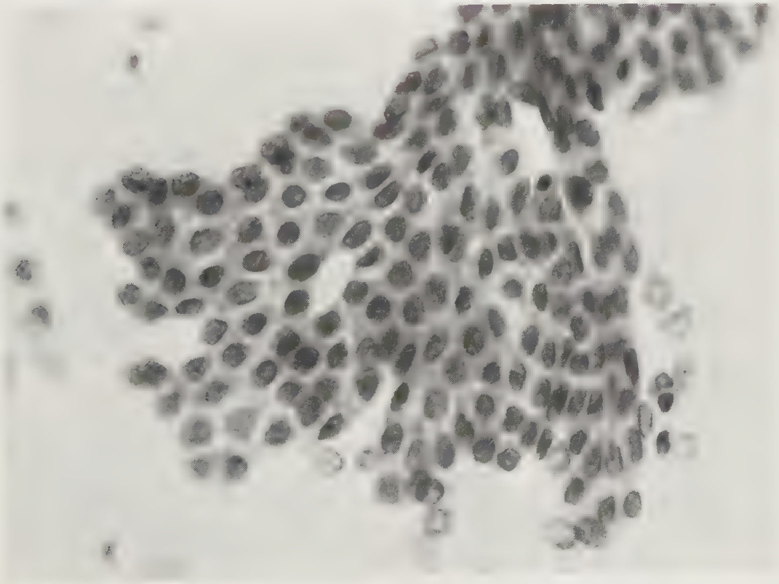

Figure 9. Normal gastric columnar cells. × 400.

number of patients with cancer missed by cytologic study is far lower than the mortality from gastric resections for such lesions, this method of approach may be life-saving for many patients. Few cancers are missed when all diagnostic procedures are expertly utilized to complement one another in conjunction with sound clinical judgment respecting decisions upon therapy.

ACKNOWLEDGMENTS

In the studies at the VA Hospital, Atlanta, the assistance and cooperation of Miss Harriet Leslie, Cytotechnologist, and Dr. Joseph Mendeloff, Chief of Laboratory Service, were appreciated greatly.

The VA Gastric Cytology Laboratory at San Francisco is grateful to Miss Fumika Ueyeda, Mrs. S. Tankersley, and Miss Jessica Ferrari for their assistance in these studies.

REFERENCES

1. Brandborg, L. L., MacDonald, W. C., Rubin, C. E., and Gottlieb, S.: Cytological diagnosis of gastric cancer by chymotrypsin lavage. The Proceedings of the Third World Congress of Gastroenterology. Recent Advances in Gastroenterology, *1*:300 1967.
2. Brandborg, L. I., Taniguchi, L., and Rubin, C. E.: Is exfoliative cytology practical for more general use in the diagnosis of gastric cancer? A simplified chymotrypsin technique. Cancer, *14*:1074, 1961.
3. Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Exfoliative cytology in non-malignant conditions of the upper intestinal tract. Acta Cytologica, 5:187, 1961.
4. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Esophageal exfoliative cytology. A neglected procedure. Ann. Int. Med., *59*:332, 1963.
5. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., Beh, J. E., and Rubin, C. E.: Exfoliative cytology screening for gastric cancer. Cancer, *17*:163, 1964.
6. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Gastric exfoliative cytology: An accurate and practical diagnostic procedure. Lancet, 2:83, 1963.
7. Raskin, H. F., Kirsner, J. B., Palmer, W. L., and Pleticka, S.: The clinical value of the negative gastrointestinal exfoliative cytologic examination in cancer suspects. Gastroenterology, *42*:226, 1962.
8. Raskin, H. F., Wenger, J., Sklar, M., Pleticka, S., and Yarema, W.: Diagnosis of cancer of the pancreas, biliary tract, and duodenum by combined cytologic and secretory methods. I. Exfoliative cytology and a description of a rapid method of duodenal intubation. Gastroenterology, *34*:996, 1958.
9. Raskin, H. F., and Pleticka, S.: The cytologic diagnosis of cancer of the colon. Acta Cytologica, *8*:131, 1964.
10. Rubin, C. E., and Benditt, E. P.: Simplified technique using chymotrypsin lavage for cytological diagnosis of gastric cancer. Cancer, *8*:1137, 1955.
11. Spjut, H. J., Margulis, A. R., and Cook, G. B.: The silicone-foam enema: A source for exfoliative cytological specimens. Acta Cytologica, 7:79, 1963.
12. Wenger, J., and Raskin, H. F.: Diagnosis of cancer of the pancreas, biliary tract, and duodenum by combined cytologic and secretory methods. II. The secretin test. Gastroenterology, *34*:1009, 1958.

Veterans Administration Hospital
4150 Clement Street
San Francisco, California 94121

Management of Pyloric Obstruction

JAMES D. BOYLE, M.D.*

HOWARD GOLDSTEIN, M.D.**

Pyloric obstruction is an important complication of peptic ulcer, often requiring surgical correction. Failure of the stomach to empty, regardless of cause, requires efficient nasogastric suction followed by serial objective assessments of the stomach's recovery.

DEFINITION

GASTRIC RETENTION. This may be caused by either *mechanical obstruction of the gastric outlet* or *simple gastric atony*. At the onset of treatment, it is difficult to tell these two conditions apart. Applying strict and conservative standards, a patient may be considered to have frank gastric retention if he has any one of the following: (1) 300 ml. of fluid remaining in the stomach at least 4 hours after a meal; (2) gastric retention of 60 per cent or more of a dose of barium sulfate administered 4 hours previously; and (3) a fasting overnight gastric residual of 200 ml. or more.

PYLORIC OBSTRUCTION. Failure of the stomach to empty is often caused by mechanical narrowing of the gastric outlet. This may occur in the antrum, pylorus, duodenal bulb, or postbulbar area. The term *pyloric obstruction* is often loosely applied to obstruction in any of these locations, although the term "gastric outlet obstruction" is preferable. Mechanical obstruction of the gastric outlet may be caused by scarring from peptic ulcer, cancer of the stomach or pancreas, or, more rarely, other lesions.

SIMPLE GASTRIC ATONY. In the absence of mechanical obstruction of the gastric outlet, the stomach may fail to empty because of impaired gastric motility. This reflex failure of gastric peristalsis and loss of the

---

*Associate Clinical Professor of Medicine, University of California School of Medicine; Chief, Gastroenterology Section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California

**Assistant Professor of Medicine, University of California School of Medicine; Assistant Chief, Gastroenterology Section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California pumping motion of the gastric antrum may be caused by local lesions, such as peptic ulcer of any site, or by distant or systemic conditions, such as uremia.

PATHOPHYSIOLOGY

Whether the stomach fails to empty because of primary motor failure or because of gastric outlet obstruction, the gastric residual progressively increases and the stomach enlarges in size. With dilatation and stretching of the gastric wall, there is further decompensation of the smooth muscle, and loss of peristalsis occurs even as a result of mechanical obstruction.

If vomiting is severe and acute, dehydration is prominent. Loss of hydrochloric acid leads to hypochloremic alkalosis. Although little potassium is present in the vomited gastric juice (7 to 10 mEq. per liter), the alkalosis causes a severe loss of potassium in the urine.[3] If the patient alternates between episodes of vomiting and copious intake of water, dilutional hyponatremia may be superimposed. Loss of extracellular fluid volume results in prerenal azotemia. Anorexia and vomiting lead to steady weight loss in many cases. Negative nitrogen balance and cachexia progressing over several weeks or more is accompanied by a contraction of the blood volume, usually without a fall in hematocrit.

ETIOLOGY

At Wadsworth Hospital, Los Angeles VA Center, from January 1, 1953, to December 31, 1963, 217 cases of gastric retention due to local gastroduodenal disease were seen[2] (Table 1). In addition, such distant conditions as hepatitis, pneumonia, and central nervous system disorders, and such systemic conditions as uremia, diabetes, and sepsis may cause transient or prolonged gastric retention.[5]

CLINICAL FEATURES

Vomiting. The classic manifestation of gastric retention is *obstructive vomiting*: the vomiting of recognizable food several hours or more after eating, becoming more severe as the day progresses. Only half of the patients had this pattern of vomiting, and surprisingly, 17 per cent had no vomiting at all.[2] Less commonly, the vomiting is either *spo-*

Table 1. *Etiology of 217 Cases of Gastric Retention*[2]

Peptic ulcer		198
Duodenal ulcer	182	
Pyloric ulcer	9	
Gastric ulcer	7	
Cancer		13
Gastric	9	
Pancreatic	4	
Adult hypertrophic pyloric stenosis		3
Acute pancreatitis		2
Annular pancreas		1

radic or is *irritative* in type (occurring within a few minutes after eating).

ABDOMINAL PAIN. While most patients have ulcer-like pain, about 10 per cent have nonspecific pain and 20 per cent have no pain.[2] The presence or type of abdominal pain is generally of no help in determining the etiology of gastric retention.

PHYSICAL EXAMINATION. Dehydration may not be clinically apparent in half of the cases. Abdominal distention is present in a minority of patients. In adults, an abdominal mass is rarely present and visible peristalsis is seldom found.[2] A succussion splash may be found in most cases, but it is too often not sought during the routine physical examination.

DIAGNOSIS

There are three overlapping stages in the diagnosis of gastric retention: suspicion of retention, verification of its presence, and search for its etiology.

1. SUSPICION OF GASTRIC RETENTION. Gastric retention should be suspected in all patients with vomiting of more than transient duration and should be considered in patients with recent unexplained anorexia and weight loss even in the absence of vomiting. Suspicion is strengthened by the presence of a succussion splash or by an upright abdominal x-ray which shows a dilated stomach filled with air and fluid. At times the diagnosis is not suspected until an upper gastrointestinal series is performed, disclosing a large stomach filled with residue and which has emptied very little 4 hours later. Such barium examinations in untreated gastric retention are unfortunate because the resulting films are generally not of sufficient diagnostic quality to determine the etiology of the retention.

2. VERIFICATION OF GASTRIC RETENTION. *Gastric Intubation.* Whenever the diagnosis of gastric retention is suspected, a large rubber Ewald tube (32F) should be passed through the mouth into the stomach, not less than 3 hours after intake of the last meal or fluid. The tube is aspirated while the patient is sitting, supine, and lying on either side, and the gastric contents are measured. The normal fasting patient has a gastric residual of less than 100 ml. of clear watery fluid, free of gross food particles. A patient with clinical symptoms due to frank gastric retention will have 300 ml. or more in his stomach 4 or more hours after the last meal, and usually 600 to 2000 ml. is found. This is usually thin opaque fluid in which are suspended fine and large chunks of recognizable food, depending on the character of the recent diet. Measurement of the gastric residual obtained with the usual nasogastric tube (16F) is unreliable, for the small distal holes of such a tube are easily plugged with food particles, and the amount of gastric retention may be seriously underestimated.

After an abnormal gastric residual is found and removed with the Ewald tube, the stomach must be thoroughly and repeatedly lavaged with water until all particles and detritus are removed and the returned washings are quite clear, before proceeding with further diagnostic and therapeutic measures.

The Saline Load Test.[1] This is a simple objective test of the stomach's ability to empty itself of a fluid load efficiently and rapidly. The normal stomach empties a large volume of instilled saline more rapidly than plain water or any other type of solution, for isotonic or slightly hypotonic saline causes the least duodenal inhibition of normal gastric emptying. For the initial saline load test, one should ensure that the stomach has been completely emptied with a 32F Ewald tube. A 16F nasogastric tube is then inserted into the stomach until the tip is 65 cm. from the nares. A bottle of 0.9 per cent sodium chloride solution is suspended 4 feet above the level of the stomach, and through an intravenous infusion set, 750 ml. of saline is dripped into the stomach as rapidly as possible (3 to 5 minutes). Thirty minutes after the beginning of the infusion, the gastric contents are aspirated with a 50 ml. urological syringe, with the patient being placed supine, upright, and on either side, repositioning the tube frequently to empty the stomach completely. The volume of the gastric aspirate is then measured.

Patients without gastric retention nearly always have saline load residues below 200 ml. A group of 69 such patients had a median residue of 60 ml., with 91 per cent falling below 200 ml. and the remaining few ranging between 205 and 385 ml. Twenty patients with untreated gastric retention had a median saline load residue of 640 ml., with a range of 370 to 750 ml.[1] Because serial daily saline load tests are helpful in assessing the response to medical treatment, we feel this test should be performed before treatment, both to confirm the results of gastric aspiration and to serve as a baseline for the follow-up tests.

3. SEARCH FOR ETIOLOGY. During the crucial initial 72 hours of medical decompressive treatment, a number of measures may be carried out in search for the specific etiology of gastric retention. A complete history and physical examination, accompanied by screening tests of the blood and urine may point towards or exclude various systemic conditions which may be the sole cause of gastric retention, such as diabetic neuropathy, uremia, increased intracranial pressure, acute pancreatitis, and viral hepatitis.

Since gastric juice is continually aspirated during this time, it is easy to send a 12-hour or 24-hour aliquot to the laboratory for determination of volume and acid concentration, which together yield the hourly output of acid. Acid values over 5 to 10 mEq. per hour strongly suggest duodenal ulcer, and values of over 20 mEq. per hour may suggest to the surgeon that he spend extra time searching diligently for an islet cell adenoma of the Zollinger-Ellison syndrome. Low acid output with a pH higher than 3 suggests gastric carcinoma. In such cases, the patient may be given a subcutaneous injection of Histalog (1.5 mg. per kg.), and the gastric juice is collected over the next 2 hours and re-examined. Absence of a significant rise in acid output in such patients strengthens the suspicion of gastric carcinoma, although the converse does not hold.

If the patient is not displaying good progress on the second day of medical decompression, as evidenced by serial saline load tests, and if a diagnosis of duodenal ulcer does not seem fairly certain, gastric exfoliative cytology should be performed at that time if reliable examinations are available.

The most pertinent diagnostic test, the upper gastrointestinal series, is often misleading and might well be avoided until the patient has recovered from gastric retention or until after the decision for surgery has already been made. To perform this radiologic examination it is necessary to interrupt the period of nasogastric suction, and it is necessary to remove the barium residual after the examination. The stomach is frequently large and atonic, emptying reluctantly into the duodenal bulb, and the resulting films frequently fail to reveal the true diagnosis. Occasionally, a patient may fail medical decompressive measures by the usual criteria, yet have ingested barium leave his stomach fairly normally. This contradiction may lead to a delay of surgery and to an unsuccessful attempt to feed the patient.

MEDICAL TREATMENT

All patients in whom a diagnosis of significant gastric retention is confirmed should receive an intensive, planned period of medical decompression and supportive measures. At the end of this time, either definitive surgery should be performed promptly or cautious progressive feedings should be begun, depending upon serial evaluative tests.

Nasogastric Suction

Medical treatment of gastric retention begins with complete emptying of the stomach through the Ewald tube, followed by meticulous water lavage until the return washings are perfectly clear. This arduous task may occupy 2 or 3 hours, but failure to remove all food particles may allow the stomach to distend subsequently because of tube blockage. The Ewald tube is replaced with a 16F nasogastric tube, inserted with the tip 65 cm. from the nares, and this is connected to a reliable continuous low-level suction apparatus. Nursing personnel should interrupt the suction every 30 to 60 minutes to syringe air or water through the tube to unblock the tube openings. If the drainage is scanty (less than 30 or 40 ml. per hour), it should be assumed that the tube is incorrectly positioned or coiled, and its proper position in the dependent portion of the stomach should be verified by x-ray and corrected as necessary.

As a general practice, 72 hours of constant nasogastric suction is the optimal duration of the test of medical decompression. Shorter periods generally fail to restore gastric motility and tone adequately. Longer periods simply exhaust the patient and seldom restore compensation when 72 hours is insufficient. Daily evaluation with the saline load test is used to assess the degree of recovery.

Replacement Therapy

Adequate replacement of pre-existing fluid and electrolyte depletion is begun immediately, and daily losses during nasogastric suction are replaced.

Total water depletion on entry to the hospital is estimated by evaluation of skin turgor, mucosal dryness, and prerenal azotemia, and this fluid is replaced with intravenous saline which is slightly hypotonic or isotonic as rapidly as the cardiovascular state permits. As soon as an adequate urine volume is confirmed, potassium chloride is added to the infusion until any serious hypokalemia has been corrected. The rate of potassium infusion is adjusted not to exceed 10 mEq. per hour initially and then at a rate of 40 to 80 mEq. per day as needed. When metabolic alkalosis is severe, it is difficult to correct significant hypokalemia with modest potassium replacement rates, for large urinary potassium losses may continue (100 to 140 mEq. per day) until sodium and chloride replacement has been achieved.

Initial determinations of serum electrolytes and creatinine are obtained and repeated daily for the next 3 days. Daily urinary losses are measured, and an aliquot of urine is saved for electrolyte determinations in patients with severe electrolyte disturbances. An electrocardiogram is obtained on admission to serve as baseline indication of hypokalemia and is repeated as appropriate.

In addition to replacing the fluid and electrolytes lost prior to hospital admission, the measured daily fluid loss in the hospital is replaced. Urine and insensible water loss are replaced with hypotonic saline, and nasogastric fluid aspirate is replaced with isotonic saline. Usually 40 to 60 mEq. of potassium is added each day.

Nutrition

All administered fluids include 10 per cent glucose, insuring an average of at least 1200 carbohydrate calories a day. Water-soluble B and C vitamins are added. Patients with more than a brief history of vomiting usually have significant loss of flesh and a negative nitrogen balance, which is further aggravated by the period of nasogastric suction. If it is necessary to prolong suction beyond 3 or 4 days, or if the patient has prominent cachexia, supplementation with intravenous casein hydrolysate or human serum albumin may be advisable as a preparation for surgery.

Patients with significant weight loss due to prolonged gastric retention develop a contracted blood volume, although this may be estimated to be "normal" when calculated on the basis of their present rather than their usual weight. Such patients frequently develop troublesome arterial hypotension at the time of surgery or in the immediate postoperative period. It has been our practice to transfuse such patients electively with 1000 ml. of whole blood slowly over the 24 hours prior to urgent surgery for gastric retention, despite the presence of a normal hematocrit.

Evaluation of Response to Therapy

Various measures have been proposed to evaluate the success of medical decompressive measures and to determine whether urgent surgery will be necessary. Many of these are quite logical, but have not been validated by a systematic study. One common method is to observe the volume of the daily nasogastric aspirate, with a decrease in volume being taken to mean a decrease of gastric retention. The amount of the aspirate, however, depends not only on the patency of the gastric outflow rate but also upon the patency of the nasogastric tube and upon the gastric secretory rate. Testing the degree of emptying of a barium meal from the stomach is objectionable, because it is not sufficiently sensitive and does not correlate well with gastric emptying of food. Some prefer simply to feed the patient at the end of medical decompression and to observe the result clinically; however, if the decompression turns out to have been unsuccessful, the feedings lead to a return of gastric decompensation, delaying the needed surgery until a second period of decompression can be completed.

We employ the saline load test to evaluate the response to medical decompression. Each morning, the nasogastric suction is interrupted just long enough to instill the 750 ml. of isotonic saline and remove it 30 minutes later, as described above. At the end of the first 24 hours of suction, a saline load test result of 200 ml. or less is an extremely favorable sign. Thus far, all of our patients with this result have tolerated progressive feedings normally at the end of the 72-hour period of suction and have done well subsequently, except for one who returned 18 months later with recurrent retention. Patients with a saline load test result of 300 ml. or more at the end of 24 hours have almost always required surgery, either at the end of the 72-hour period of suction or soon thereafter. We have noted only two exceptions to this "rule." The 24-hour test value is therefore useful in predicting the eventual response to treatment and allows one to prepare expectantly for likely surgery (Fig. 1).

Regardless of the result of the 24-hour saline load test, nasogastric

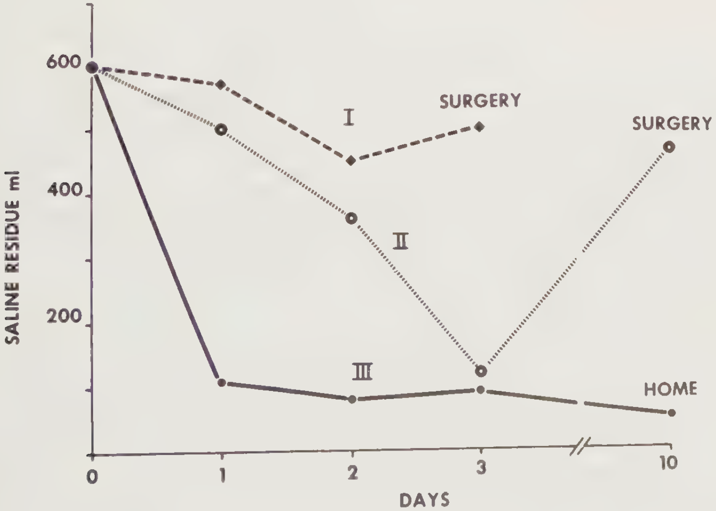

Figure 1. Typical serial results of the saline load test are shown just before beginning nasogastric suction (day 0) and on subsequent days. Patients with gastric retention fall roughly into 3 groups. Group I: Persistent abnormality, requiring surgery. Group II: Abnormal at 24 hours, but normal at 72 hours, with relapse after stopping suction, requiring surgery. Group III: Value returns to normal at 24 hours, with clinical recovery.

suction should be continued for a full 72 hours, at which time the test should be repeated. A value of 400 ml. or more at this time is a clear indication for surgery. If values of less than 200 ml. are obtained, both at 24 hours and at 72 hours, the patient is begun on small liquid feedings and progressed each day until a full diet is taken. Each morning for three mornings, and then with decreasing frequency, a nasogastric tube is passed in the fasting state, and the morning residual is measured and a saline load test is performed.

If the 24-hour value is over 200 ml. or if the 72-hour value is between 200 and 400 ml., the patient is also put on a liquid diet which is progressed cautiously with daily monitoring of the morning residual and the saline load test. If definite signs of gastric retention recur, the patient is immediately begun on nasogastric suction after Ewald tube lavage, and surgery is performed at 48 hours.

Late Management

After recovery from gastric retention, radiologic and other diagnostic studies are completed to permit an exact etiologic diagnosis and appropriate specific therapy for the underlying lesion.

Approximately 15 per cent of the patients developed a recurrence within the first year after the initial episode of medically managed gastric retention due to duodenal ulcer, and another 10 per cent had a recurrence in the next 8 years, in one retrospective series.[2] While such a recurrence rate is significant, recurrence is far from inevitable. Patients with an uneventful recovery from a single episode of gastric retention associated with duodenal ulcer are not recommended for elective ulcer surgery unless there are other compelling indications.

SURGICAL MANAGEMENT

PREOPERATIVE PREPARATION. An acceptably low mortality for the urgent surgery of gastric retention depends upon (1) preoperative medical decompression of adequate duration, and (2) adequate preoperative fluid and electrolyte replacement. In our series,[2] only 1.3 per cent of those with adequate decompression and replacement therapy died after surgery, while 19 per cent of those whose preoperative treatment was inadequate in one or both respects died after surgery. Failure to decompress the stomach for 48 to 72 hours before surgery leaves the stomach atonic and dilated. Surgical anastomosis is difficult and postoperative emptying problems are more frequent.

CHOICE OF SURGERY. When gastric retention is associated with peptic ulcer, it appears that most types of ulcer operations provide satisfactory relief of gastric retention. While some observers find a distressingly high incidence of postoperative gastric retention or stomal dysfunction following vagotomy and drainage,[4] in another series this complication was attributed to inadequate preoperative decompression rather than vagotomy.[2] With the frequency of incomplete section of the vagus nerves, one might speculate that a more effective ulcer operation such as vagotomy and antrectomy might be preferable to simple vagotomy and drainage in the treatment of this serious complication of peptic ulcer.

SUMMARY

Gastric retention may be caused by mechanical obstruction or simple gastric atony. Both are treated with gastric lavage, 72 hours of nasogastric suction, and replacement of fluid and electrolytes. The saline load test is a convenient method of evaluating response to medical treatment. Surgery is promptly performed in those cases in which a formal trial of medical treatment has failed and in which the retention is believed due to local gastroduodenal disease with mechanical obstruction.

REFERENCES

1. Goldstein, H., and Boyle, J. D.: The saline load test – a bedside evaluation of gastric retention. Gastroenterology, *49*:375-380, 1965.
2. Goldstein, H., Janin, M., Schapiro, M., and Boyle, J. D.: Gastric retention associated with gastroduodenal disease: a study of 217 cases. Amer. J. Digest. Dis., *11*:887-897, 1966.
3. Howe, C. T., and LeQuesne, L. P.: Pyloric stenosis: The metabolic effects. Brit. J. Surg., *51*:923-932, 1964.
4. Kraft, R. O., Fry, W. J., and Deweese, M. S.: Postvagotomy gastric atony. Arch. Surg., *88*:865, 1964.
5. Rimer, D. G.: Gastric retention without mechanical obstruction. Arch. Int. Med., *117*:287-299, 1966.

Veterans Administration Center
Los Angeles, California 90073

Malabsorption

JAMES D. FINKELSTEIN, M.D.*

During the last two decades our knowledge of the physiology of intestinal absorption and the pathophysiology of malabsorption syndromes has progressed in a fashion equalled by few other areas of biomedical research. In large measure this is due to the availability of new techniques and tools, including radioisotopes, surviving in vitro preparations of small intestine, and peroral biopsy instruments. However, it is likely that this remarkable progress can be attributed equally to a noteworthy interaction between nonclinical scientists and clinical investigators. Because of this dialogue there has been little time lost in applying new findings to clinical situations, and, conversely, numerous fundamental problems have been suggested and even resolved by patient studies. The net result for the clinician is an increased understanding of the mechanisms of malabsorption, an increased ability to predict or anticipate when these mechanisms may be significant, an increased capability to document the existence of these disorders, and an increased capacity to restore normal intestinal function.

An understandable increase in specialization has accompanied the rapid expansion of knowledge. This, in turn, has had some adverse side effects. Symposia have replaced general review articles and substantial monographs have appeared. In short, the dialogue, which has been so productive, may be in jeopardy. In particular, the clinician is finding it increasingly difficult to keep informed about recent advances. It is my hope that this paper will assist the clinician in the physiological interpretation of problems in intestinal absorption. Conversely, I hope to present material which will enable the nonclinical investigator to evaluate the clinical applications of recent work, the problems which remain, and the availability of clinical material which may assist in future studies.

Malabsorption can be defined as an abnormal net transfer of substrate from the intestinal lumen to the body. In its broadest sense, malabsorption describes not only a decrease in the absorption of exogenous substrate, but also an increase in the loss of endogenous substrates into the gut lumen. There is no reason to exclude from this category syndromes characterized by increased intestinal absorption, but, by unwritten convention, clinical problems associated with hyperabsorption (vitamin D intoxication, idiopathic hypercalciuria, sarcoidosis, hemochromatosis, Wilson's disease) are not considered as malabsorptive states. In any event, malabsorption may be symptomatically significant or only chemically demonstrable. It may be generalized and include many if not all substrates, or it may be specific to a single substrate. The clinical significance and the substrate specificity are determined by the nature, location, and extent of the lesion.

---

*Chief, Hepatology Section and Biochemistry Research Laboratory, Veterans Administration Hospital; Assistant Professor of Medicine, George Washington University, Washington, D.C.

NORMAL ABSORPTIVE PROCESS

General Considerations

The reactions leading to the absorption of dietary factors are listed in Table 1. Few nutrients occur naturally in an absorbable form, so that the first phase of absorption is the preparation of a suitable substrate—a preparation that might require the presence of specific digestive enzymes either secreted into the intestinal lumen by the salivary glands, stomach, and pancreas or located on the absorptive surface itself. These enzymes reduce polysaccharides to mono- and disaccharides, triglycerides to monoglycerides and free fatty acids, and proteins to amino acids and simple polypeptides. They also free other substrates from moieties to which they were bound. A second type of mechanism activates substrate for absorption by binding to a specific co-factor. The role of intrinsic factor in vitamin B_{12} absorption typifies this process. Thirdly, the physical state of the substrate may be changed in the absence of chemical alterations. This mechanism, of great significance in lipid absorption, will be amplified below. Finally, the pH of the intestinal contents must be suitable for the absorption of the substrate.

Once it has been converted to the appropriate form, the substrate must come into contact with an intact absorbing surface. In this context "intact" implies not only structural but also biochemical integrity.[30] Substrate-specific transport mechanisms which enable the intestinal mucosa to transfer compounds against concentration (or electrochemical) gradients must be operative. Such active transport processes, in contrast to simple diffusion, require the expenditure of energy. In simple diffusion, substrate moves down a concentration gradient and the rate of its migration is limited by the concentration differences between the two compartments, and by the surface area and physical properties of the membrane. Both active transport and passive diffusion

Table 1. *The Normal Absorptive Process*

- Preparation of substrate
  - Enzymatic digestion
  - Specific binding
  - Change in physicochemical state
  - pH adjustment
- Contact with intact mucosal absorbing surface
- Transport across mucosal cell to vasculature

are operative in man, but the relative significance of the two under physiological conditions is uncertain. Some pertinent information can be developed from studies of specific states. Disabilities which attend failure of specific transport mechanisms suggest that passive diffusion alone is insufficient for adequate absorption. Calcium absorption is inadequate in vitamin D deficiency, as is vitamin B_{12} absorption in pernicious anemia. Defects of the monosaccharide transport system (glucose malabsorption), the methionine transport system (methionine malabsorption), the dibasic amino acid transport system (cystinuria), and the monoamino-monocarboxylic acid transport system (Hartnup disease) are all associated with an excess accumulation of substrate in the intestinal lumen.

After the substrate has been absorbed from the lumen, it must be transported across the mucosal cell to the effluent vessels. A second transport mechanism – located within the cell, perhaps at its submucosal pole – may be necessary to transfer the substrate out of the mucosal cell. Evidence for a "two-step mechanism" has been found by in vitro studies of calcium, iron, and amino acid absorption. Other substrates are chemically altered within the intestinal mucosa before release from the cell. Lipoprotein synthesis, for example, is a prerequisite for triglyceride transfer to the lymphatics, and some steroids and bilirubin appear to leave the cells as glucuronide conjugates.

With these general considerations as an outline we can now consider briefly the specific mechanisms involved in the absorption of several substrates from the intestinal lumen.

Absorption of Carbohydrates[12, 26]

Starch represents the bulk of dietary carbohydrates, but significant quantities of disaccharides (sucrose, lactose) and monosaccharides (glucose, fructose) may also be found. The major portion of starch (amylopectin) is composed of chains of glucose molecules bound together in 1,4 α linkage.

The molecule also has a significant number of branch points (1,6 α linkages). Amylases secreted by the salivary glands and pancreas hydrolyze the 1,4 α bonds but not the branch points. The products of these reactions are maltose, maltotriose, free glucose, and α-limit dextrins (which contain the unaffected 1-6 α bonds). This ends the intraluminal phase; further digestion is achieved at the mucosal cell surface by specific enzymes. The α-dextrin is hydrolyzed by isomaltase, and maltose and maltotriose are hydrolyzed by the maltases. Similarly dietary sucrose and lactose, unaffected by the intraluminal amylases, are substrates for intestinal sucrase and lactase respectively. In each instance the products of hydrolysis are the constituent monsaccharides: maltose, maltotriose, and α-dextrin yield glucose; sucrose yields glucose and fructose; and lactose yields glucose plus galactose. It seems likely that these monosaccharide products are not released into the intestinal lumen. Absorption occurs immediately after hydrolysis at the cell surface. Glucose and galactose share a common active transport mechanism which is dependent on the presence of Na^+, while fructose is absorbed by passive diffusion.

Absorption of Protein[9,25]

Protein digestion and absorption is, in many respects, analogous to carbohydrate absorption. Ingested protein plus a considerable quantity of endogenous protein is hydrolyzed to free amino acids and small polypeptides by the action of the pancreatic, and to a lesser extent gastric, proteases. The small intestinal mucosal cell possesses dipeptidases, similar in function to the disaccharidases, and hydrolysis of the dipeptides occurs at or within the luminal border of the cell.[22] The resultant amino acids are then actively transported into the cell. The number of specific amino acid transport mechanisms is as yet undefined, but at least three seem likely. These transport (1) neutral amino acids, (2) dibasic amino acids, and (3) imino acids, glycine and N-methylated amino acids. The dicarboxylic acids are thought to be absorbed passively. The possibility of further subdivision, particularly of the first group, seems likely. Certainly, the syndrome of isolated methionine malabsorption is not explicable by the current classification, since methionine is reported to have a high affinity for the neutral amino acid transport mechanism.[1]

Absorption of Fats[5,15,20,28]

The mechanism for intestinal lipid absorption differs markedly from that for carbohydrates and proteins. The complex reactions and interactions involved perhaps explain the frequent occurrence of fat malabsorption in diseases of the digestive system — so that steatorrhea has become synonymous with malabsorption to many clinicians. Ingested fat is a complex mixture of triglycerides, phospholipids, sterols, and the fat-soluble vitamins A, D, E, and K. After dispersion in the stomach, these compounds are emulsified in the presence of bile salts in the proximal duodenum. The triglycerides in emulsion are then hydrolyzed by pancreatic lipase to yield free fatty acids and monoglycerides. In addition to these products the luminal contents include bile salts with which, at appropriate concentrations and pH, they form micelles. Micelles can be envisioned as lipid lakes in an aqueous solution. In contrast to emulsions they are small, chemically well defined, and physically oriented so that the hydrophilic groups are directed toward the water phase and the hydrophobic groups (lipid-soluble) are interior. Other lipids, such as cholesterol and fat-soluble vitamins, can dissolve in this lipid phase. It must be re-emphasized that optimal micelle formation requires not only bile salts but the free fatty acids and monoglycerides which result from hydrolysis of ingested triglyceride.

At present, the best evidence suggests that lipid compounds are absorbed passively from the micellar form in contact with the small intestinal mucosa of the midgut. The bile salts are not absorbed at this level and pass to a more distal site where an active transport process operates. Within the intestinal mucosal cell, absorbed free fatty acids are re-converted to triglycerides by esterification of absorbed glycerol or glycerol derived from glucose. Absorbed monoglyceride is also converted to triglyceride either by direct acylation with free fatty acids or after prior hydrolysis to free fatty acids and glycerol. The re-synthesized triglyceride and other absorbed lipids are then coupled with protein to form chylomicrons, an obligatory step before the absorbed fats can enter the intestinal lymphatics.[33]

Medium chain triglycerides (MCT), which contain fatty acids of 10 carbon atoms or less, are handled differently. MCT are absorbed after hydrolysis to glycerol and fatty acids. Unlike long chain fatty acids, they are not re-esterified to triglycerides and do not require chylomicron formation for exit. Rather, they enter the portal blood as albumin-bound free fatty acids. The rate of hydrolysis by pancreatic lipase of MCT also exceeds that of the normal dietary triglycerides. These differences form the rationale for the frequent use of MCT in patients with fat malabsorption.[18]

Salt and Water Absorption[11, 27]

Approximately 8.5 liters of fluid containing 750 mEq. of salt enter the upper small intestine of man each day. The largest part of this volume (80 per cent) is derived from secretions into the gastrointestinal tract. Normal stool water volume is about 100 ml. per day, with Na^+ and K^+ concentrations of 25 to 49 and 80 to 132 mEq. per liter, respectively. More than 8 liters of fluid containing approximately 750 mEq. of Na^+ are therefore absorbed daily. Since the colon removes 500 ml. of fluid and 70 mEq. of Na^+, it is clear that most water and salt absorption occurs in the small intestine. Fordtran describes the many mechanisms believed to be operative.[10] In the proximal small intestine considerable quantities of water and salt are passively absorbed due to the osomotic gradients established by the active transport of nonelectrolytes (glucose, amino acids, etc.). Additional Na^+ is absorbed in the proximal intestine in association with the active secretion of H^+ (or active absorption of HCO_3^-). Active transport of Na^+ accounts for the absorption of this ion in the ileum and colon. In these distal areas Cl^- absorption and HCO_3^- secretion appear coupled, so that exchange can occur without net anion movement. At all levels of the gut, K^+ movement seems to be a passive process with diffusion from the lumen in the duodenum and diffusion into the lumen distally. It follows that in any condition in which there is malabsorption of nonelectrolytes, considerable quantities of water and electrolytes may be retained in the intestinal lumen, and diarrhea with salt and water depletion may be anticipated.

Calcium Absorption

Ionic calcium is absorbed in the proximal intestine by means of an active transport mechanism which is dependent on vitamin D. The mechanism responds to nutritional needs. One finds, for example, greater absorption in calcium-depleted animals. The mechanism is also sensitive to hormones. There is a marked decrease in transport following hypophysectomy (growth hormone deficiency) or administration of adrenal glucocorticoids, thyroxine, and estrogen.

Iron Absorption[3]

Apparently two mechanisms exist for iron absorption. One system transports inorganic iron[23] and the other transports heme iron.[1, 32] In vitro and in vivo studies in numerous species indicate that inorganic iron transfer requires two discrete steps – uptake into the mucosal cell and transfer from the cell to the blood stream. The second step is specific for ferrous ion, whereas mucosal uptake occurs with the ferric as well as the ferrous form. Since the ability of the body to eliminate excess iron is limited, there is a need for considerable regulation of iron absorption. This is accomplished at both steps, but the more sensitive mechanism is the step which transfers iron out of the absorbing cell. This excess iron, absorbed but not transferred, is lost in the stool when the mature intestinal cell is desquamated at the villous tip. The mechanism which transmits information concerning iron stores and needs to the absorptive cell is unknown. Nevertheless, the system can adapt to the level of iron in the diet, to blood loss, and to the increased requirements of pregnancy.

Absorption of Water-Soluble Vitamins[24]

Vitamin B_{12} absorption is the result of an integrated series of reactions.[11] The dietary vitamin is digested free of protein moieties and is combined with intrinsic factor (IF) which is secreted by the stomach. The IF-B_{12} complex passes to the distal ileum, where it attaches to specific receptor sites. This binding process requires calcium ions and an alkaline pH. Subsequent steps are obscure. Most likely, an intestinal "releasing factor" breaks the IF-B_{12} bond and the B_{12} is absorbed. The fate of IF is not known. Some absorption of vitamin B_{12} may occur by passive diffusion after massive oral doses of the vitamin.

Although malabsorptive states frequently affect folic acid (pteroylglutamic acid) absorption,[21] little is known of the physiology of its intestinal transport.[14] Dietary folate occurs in many forms and the form(s) in which it is absorbed is unknown. Similarly we do not know whether an active transport mechanism is involved nor in which form the vitaman leaves the mucosal cell.

Even less is known about the absorption of the other B vitamins and ascorbic acid. Some evidence suggests that there is an active transport mechanism for thiamine in human intestine.

Localization of Absorptive Mechanisms[2, 19]

The various transport mechanisms differ from one another not only in their mode of action but also in their location along the length of the small intestine. The anatomical site of a mechanism frequently determines its involvement in pathological states. Some care must be exercised in defining these sites, and extrapolation from species to species is often misleading. In addition, the most active site, defined by laboratory studies, may not be the most significant site under physiological conditions. A highly active distal locus, for example, could be insignificant if the bulk of substrate is absorbed proximally by passive diffusion. We must also consider the finding that lesions (most often extirpation) of one area of small intestine may lead to adaptive changes in uninvolved segments.[8, 19] Jejunal alterations follow iliectomy, and ileal changes follow jejunectomy.

Despite the above reservations, a tentative localization of absorption

Table 2. *Distribution of Absorptive Surfaces in the Small Intestine*

PROXIMAL		MID	DISTAL
Calcium		Lipids	Vitamin B_{12}
Iron		Amino acids	Bile salts
Folic acid			
B vitamins			
	Monosaccharides		
	Xylose		

sites is presented in Table 2. In general, substrates that are transferred by passive diffusion will be absorbed proximally because of (1) higher concentrations in the lumen; (2) relatively greater surface area; and (3) greater water permeability (and theoretical surface "pore" size) proximally.

MALABSORPTION

A pathological process which disrupts any of the absorptive mechanisms summarized above will lead to malabsorption of a particular substrate. If the disrupted mechanism is common to several substrates (for example, pancreatic secretion), or if the pathological process involves more than one absorptive mechanism, the malabsorption will involve several substrates. In short the pattern of malabsorption is determined by the nature, extent, and location of the pathological process.

The pathophysiological mechanisms which can result in malabsorption are included in Table 3.

Extraintestinal Causes of Malabsorption

Exclusion of co-factors which are necessary for the preparation of a substrate for absorption defines these disorders, which are associated with diseases of the stomach, pancreas, and hepatobiliary system.

Gastric insufficiency (atrophic gastritis, postgastrectomy, pernicious anemia) may result in deficient secretion of both hydrogen ion and intrinsic factor. The absence of intrinsic factor leads to vitamin B_{12} malabsorption, but the results of deficient hydrogen ion secretion are less clear.

Table 3. *Pathophysiological Mechanisms of Malabsorption*

- Extraintestinal
  - Exclusion of adjuvants to absorption from gastrointestinal lumen
- Intestinal
  - Reduced contact time, mucosa and substrate
  - Reduced intestinal absorptive surface
  - Reduction of intracellular digestive enzymes
  - Impaired specific transport mechanisms
  - Impaired vascular outflow from intestine
  - Presence of abnormal flora
    - Competition for substrate
    - Elaboration of abnormal metabolites
  - Excessive transfer, gut to lumen

Since calcium and iron are absorbed in their ionic forms (favored by acid pH), some inhibition of absorption might be anticipated with gastric failure. Similarly, since the digestive enzymes are pH-sensitive, they may not function optimally with excess alkalinity of the proximal small intestine. Excessive gastric acid secretion (Zollinger-Ellison syndrome) also results in malabsorption, possibly the result of duodenal pH changes. In this instance excessive acidity lowers the pH below that optimal for enzyme activity (particularly pancreatic lipase) and steatorrhea ensues.

In pancreatic insufficiency (chronic pancreatitis, postpancreatectomy), the deficiency of digestive enzymes results in a generalized malabsorption of complex carbohydrates, lipids, and proteins. Even simple lipids, such as the fat soluble vitamins, may be malabsorbed. Inadequate micelle formation in the absence of the monoglycerides and free fatty acids (derived from dietary triglyceride by the action of pancreatic lipase) provides a possible explanation.

Biliary obstruction leads to the exclusion of bile salts from the intestinal lumen and generalized steatorrhea could be anticipated secondary to the failure of micelle formation. The clinical picture is complicated by other roles of intraluminal bile salts.[6] In addition to micelle formation, these compounds (1) enhance the action of pancreatic lipase (perhaps by reducing the enzyme's optimal pH to the physiological range); (2) enhance triglyceride resynthesis in the mucosal cell; and (3) regulate cholesterol synthesis by the intestine. The absence of this inhibition of synthesis probably explains the hypercholesterolemia of biliary obstruction—an apparent paradox in association with the lipid malabsorption. The malabsorption which occurs with hepatitis is probably due to direct involvement of the small intestine by the disease, and the malabsorption which is associated with cirrhosis may represent hepatobiliary failure, but pancreatic, gastric, and intestinal dysfunction may play a role.

Reduced Contact Time, Mucosa and Substrate

Any disease associated with a marked decrease in small intestinal transit time might result in a malabsorption syndrome involving any or all substrates. Since this is usually an acute process, little attention has been paid to absorptive problems with the exception of water and electrolyte imbalance. It is likely that the malabsorption associated with the carcinoid syndrome is explicable by a reduced contact time.

Reduced Intestinal Absorptive Surface

Examples of malabsorption due to this mechanism are frequently encountered (postresection, regional enteritis, neoplasm, fistulous bypass). The nature of the absorptive defect is determined by the location and the extent of the lesion. Involvement of the distal ileum results in malabsorption of vitamin B_{12} and bile salts. If the bile salt deficiency is severe, a secondary steatorrhea may occur.[16] Patients with inadequate ileal surface also have a reduced ability for fat absorption, which may be demonstrable only at intakes high enough to exceed the capacity of a normal jejunum and proximal ileum. Proximal mechanisms are not affected, and the appearance of xylose malabsorption in a patient with regional enteritis is an indication of the presence of "skip areas" of involvement in the duodenum and jejunum.

Loss of the proximal absorptive surface may lead to malabsorption of calcium (osteomalacia), folate, and xylose. Steatorrhea may also occur, but since the process involving the proximal intestine often involves the contiguous structures, it is difficult to define the exact mechanism for the fat malabsorption. For example, a gastrojejunostomy not only involves bypass of the duodenum, but also entails the diversion of food flow from the biliary and pancreatic stoma and the possibility of bacterial overgrowth in the afferent loop. The surgery frequently includes partial gastrectomy and vagotomy, which further confuse the picture.

Loss of the midpart of the small intestine can be accompanied by steatorrhea and protein malabsorption. Since the ileum can compensate in part for the lost jejunum, the degree of malabsorption is determined by the extent of the lost surface as well as the nature of the diet.

It is possible that the malabsorption of nontropical sprue (gluten enteropathy) can be explained by the diminished surface area consequent to the loss of villous and microvillous structures. The attractiveness of this hypothesis is limited by the finding that, with therapy, normal absorptive function may appear before anatomical improvement.

Absence of Intracellular Digestive Enzymes

Deficiencies of the mucosal disaccharidases are the prime examples of this pathophysiological mechanism. Peternel discusses this problem at length in another article (see p. 1355). At present there is no evidence for an analogous set of syndromes due to dipeptidase deficiency, but it is likely that some will be found. We must consider, for example, the possibility that nontropical sprue is the result of an inability to digest a simple peptide derived from gluten. The undigested peptide, functioning as either a direct toxin or an antigen, could then cause the observed pathology.

Impaired Specific Transport Mechanisms

This process leads to malabsorption of only those substrates which share the specific mechanism. Examples of this category are usually rare, inherited defects which are of great interest to investigators. Several syndromes of this type are listed in Table 4. The clinical picture is determined by either a systemic deficiency of the substrate (calcium, vitamin B_{12}, or lipids – including fat-soluble vitamins) or by the action of intestinal bacteria on unabsorbed substrate (glucose-galactose, methionine). In some instances the gastrointestinal findings are interesting but the clinically significant transport defect is in the kidney (cystinuria).

Impaired Vascular Outflow From the Intestine

Obstruction of the regional lymphatics may result in steatorrhea and enteric protein loss (see below). Absorption of other substrates should not

Table 4. *Diseases Related to a Deficiency in a Specific Transport Mechanism*

SUBSTRATE	DISEASE	PATHOGENESIS
Calcium	1. Rickets 2. Vitamin D–resistant rickets	1. Vitamin D deficiency 2. Calcium transport mechanism refractory to normal levels of vitamin D
Monohexoses	Glucose-galactose malabsorption	Failure of active transport system in intestine
Methionine	Methionine malabsorption (Oasthouse syndrome)	Failure of active transport system in intestine
Diabasic amino acids and cystine	Cystinuria	Failure of active transport system, intestinal and renal
Neutral amino acids	Hartnup disease	Failure of active transport system, intestinal and renal
Lipids	A-beta-lipoproteinemia	Inability to form chylomicrons due to failure to synthesize β-lipoproteins. Lipid cannot exit from intestinal mucosa.
Vitamin B_{12}	1. Pernicious anemia, juvenile or adult 2. Intestinal malabsorption of vitamin B_{12} 3. "Releasing factor" deficiency	Failure of intrinsic factor synthesis Absence of ileal receptor sites Possible failure of intestinal factor to cleave IF-B_{12} complex.
Chloride	Congenital alkalosis with diarrhea (congenital chloridorrhea)	Failure of intestinal Cl^- absorption

be affected except as a possible consequence of local edema. Lymphatic obstruction explains the malabsorption of fat seen with tumor involving the mesenteric root and with intestinal lymphangiectasia. It is possible that this mechanism also applies in Whipple's intestinal lipodystrophy, although generalized malabsorption is characteristic of this syndrome.

The venous hypertension of congestive heart failure and restrictive pericardial disease might also cause malabsorption. Whether this is directly related to venous obstruction or to a secondary increase in lymphatic pressure is uncertain. So is the pattern of the malabsorption. But we should consider the possibility that absorptive defects will limit the efficacy of the oral medications which are frequently employed in these situations.

Abnormal Intestinal Flora[7, 29]

Bacterial overgrowth is commonly found in disorders of small intestinal motility and in stagnant loops of intestine. Specifically, abnormal flora is found in diverticula and blind loops, behind strictures and partial obstructions (regional enteritis, postirradiation, lymphoma), and in the presence of visceral neuropathy (diabetes mellitus, amyloidosis, scleroderma). Loops of bowel need not be "blind" in the classic sense, since overgrowth has been observed in the duodenal (afferent) limb of gastrojejunostomies. The bacteria may interfere with intestinal absorption by competing for substrates or by elaborating metabolites which disrupt normal absorption. The relative importance of these two possibilities is unknown. The malabsorption of vitamin B_{12} does seem to be the result of competitive uptake by Escherichia coli. On the other hand, recent studies suggest that the steatorrhea may be due to bacterial hydrolysis of bile salts to free bile acids which do not form micelles.

Other parasites may induce defects. Infestation by fish tapeworm (Diphyllobothrium latum) results in malabsorption of vitamin B_{12}, and patients with giardiasis may have a generalized malabsorption.

Excessive Transfer from Body to Lumen

Loss of any substrate from the bowel is possible if there is a failure to absorb normal secretions or a presence of excessive secretions. At present, this pathophysiological mechanism is of clinical significance only in the instances of salt and water loss and of enteric protein loss. Protein-losing enteropathy is not an isolated entity but is a syndrome which may accompany any inflammatory, neoplastic, or vascular disease of the intestinal tract.[31] However, the massive loss of protein with a resultant hypoproteinemia and anasarca may dominate the clinical picture. In contrast to renal protein loss, intestinal "leakage" is relatively nonspecific and all species of protein are lost. The typical finding includes hypoglobulinemia as well as hypoalbuminemia.

THE DIAGNOSIS OF MALABSORPTION

The possibility of a malabsorption syndrome may be suggested by data obtained from the history, the physical examination, or the routine laboratory tests, but the diagnosis is always confirmed by chemical means. The central importance of the laboratory should not be interpreted as an indication that highly specialized facilities are necessary. Some specific studies are required, but routine procedures still afford considerable help.

History and Physical Examination

The diagnosis of malabsorption should be suspected under the following circumstances: (1) unexplained weight loss or the failure to regain weight after abdominal surgery; (2) unexplained diarrhea; (3) metabolic deficiencies (megaloblastic anemia, metabolic bone disease, etc.) despite adequate intake; and (4) the presence of a disease which may be associated with malabsorption (pancreatitis, diabetes mellitus, scleroderma, etc.). Particular care must be exercised in developing the history of weight loss, food intake, and bowel habits. Fatty, foul, and floating stools are not a sine qua non for the presence of steatorrhea. The family history and the patient's childhood history may be significant because of the frequency of inherited or congenital disorders. For example, adult non-tropical sprue may reappear after an asymptomatic interval in a patient who had childhood celiac disease. The physical examination may provide evidence of weight loss, of nutrient deficiency (lesions of skin and hair, glossitis, cheilosis, anemia, tetany, edema), and of an underlying disease.

Laboratory Tests

The biochemical studies document malabsorption of the suspected substrate(s) and define the pattern of malabsorption of other substrates. Two types of tests are employed. Indirect evidence for malabsorption may be adduced from evidence for the deficiency of a substrate (or its derivatives) in body tissues. However, this presupposes a period of malabsorption sufficient to deplete the body stores. If parenteral administration corrects the deficiency which did not respond to oral feeding, then malabsorption is likely. A more direct means of measuring absorption is to employ tolerance tests in which the substrate is fed and the amount absorbed is estimated by determining the residual in the stool or the increase in urine and blood levels.

Studies of Lipid Absorption

The presence of steatorrhea is best determined by the direct chemical measurement of fecal fat excretion during a period of constant fat intake. There is some variation between laboratories, but the upper limit of normal is 5 to 7 per cent excretion while ingesting 100 gm. of fat. This technique, while esthetically traumatic, should be routine since it is not adequately replaced by studied utilizing ^{131}I-labelled lipids. Nutritional studies can be used to evaluate lipid absorption. A low serum carotene level usually indicates steatorrhea. The prothrombin time test is another valuable tool and is available routinely. If this value is prolonged, responding to parenteral but not oral therapy, malabsorption of vitamin K is probable. The interpretation of the serum cholesterol and the serum calcium and phosphorus may be helpful but difficult. Hypocholesterolemia may be due to bile salt malabsorption as well as lipid malabsorption. Similarly, a low or normal serum calcium associated with a low serum phosphorus suggests calcium malabsorption, but does not differentiate between a primary defect in the duodenal mechanism and a secondary defect due to vitamin D malabsorption (steatorrhea). Vitamin A tolerance tests are rarely employed. In a limited personal experience, I have found them to be reproducible and to reflect lipid absorption as measured by direct determination of fecal fat.

Studies of Protein and Amino Acid Absorption

There are investigational but not routine tests of protein and amino acid absorption. Hypoalbuminemia commonly occurs. This may be secondary to amino acid deficiency, although low albumin values may also result from decreased synthesis (hepatic disease, chronic illness) or augmented catabolism. The presence of hypoglobulinemia together with hypoalbuminemia suggests a protein-losing enteropathy, which is demonstrable by measuring the loss into the lumen (stool) of radioactive label from protein which is injected intravenously.[31] The best system appears to be that employing ^{51}Cr-albumin.

Studies of Carbohydrate Absorption

All tests in this category employ tolerance techniques. The carbohydrate (starch, disaccharide, or monosaccharide) is fed (usually 1 gm. per kg. body weight) and a rise in blood sugar of at least 25 mg. per 100 ml. is considered normal. Using these tests in combination, we can distinguish pancreatic amylase deficiency (starch intolerance), disaccharide intolerance, and defects in the intestinal transport of glucose (and galactose). But there are difficulties. Flat glucose tolerance curves may result from rapid utilization as well as from malabsorption of the sugar. More significantly, glucose absorption is an insensitive indicator of intestinal disease. The capacity of the transport is so great that gross disease is required before abnormal tests can be obtained. For this reason the xylose tolerance test has been utilized with increasing frequency. *d*-Xylose, a pentose, might not be transported by the normal hexose mechanism and is, contrary to original reports, partially metabolized. In spite of its limitations this test is probably the simplest and most sensitive tool for evaluating proximal intestinal function. A 5-gm. dose is adequate and spares the patient the side effects which may occur with a 25-gm. load. After either dose, a person with normal intestinal and renal function will excrete 20 per cent within 5 hours. Division of the sample into 2-hour and 3-hour specimens may be a more sensitive test than the single collection method.

Studies of Vitamin B_{12} and Folate Absorption

Vitamin B_{12} absorption can be measured by a variety of tests which utilize radiocobalt-labelled vitamin. If malabsorption is present, modifications of the absorption study should identify the pathophysiological mechanism. Intrinsic factor deficiency is reversed by intrinsic factor, bacterial overgrowth by antibiotics, and "releasing factor" deficiency by human intestinal aspirates. Malabsorption of vitamin B_{12} due to deficient ileal receptor sites is irreversible. Folate tolerance tests can be employed using the tritiated vitamin. Microbiological assays are also available for the measurement of serum and tissue levels of both folate and vitamin B_{12}.

If the above tests are not available, the clinician can rely on the routine laboratory for data indicative of malabsorption of either factor. A megaloblastic marrow, unresponsive to an adequate diet (or low-dose oral supplements) but responsive to daily injections of either 1 mg. of vitamin B_{12} or 100 to 200 μg. of folic acid, suggests the presence of malabsorption of the effective agent. At these dosages folate will not mask vitamin B_{12} deficiency, nor will vitamin B_{12} obscure folate deficiency.[13]

Studies of Iron and Calcium Absorption

Several groups have described direct tests for measuring the absorption of radioactive isotopes of these ions, but they are difficult to interpret. For routine purposes, malabsorption can be identified by demonstrating a deficiency state which is responsive to parenteral, but not oral, therapy. Adequate criteria for iron deficiency are microcytic anemia, low serum iron, and reduction of the marrow iron stores. The picture of calcium deficiency is less well defined. A low or normal serum calcium is usually accompanied by a low serum phosphorus (secondary hyperparathyroidism). A modest elevation of serum alkaline phosphatase is common and the level of this enzyme may increase further initially when calcium absorption improves. Because of the pathophysiology underlying the chemical changes, an infusion of calcium should (1) raise the serum phosphorus and (2) be retained in excess of normal. This test, however, has not proved effective in differential diagnosis. Bone biopsy, which is simple and well tolerated, is a more informative index of metabolic bone disease than is radiographic examination.

Patterns of Malabsorption

If we know which substrate a patient can absorb, we can define a pattern of function which localizes the defect and assists in establishing the etiology of the dysfunction. Table 5 illustrates several patterns which are rarely as clear in clinical situations. Several practical points are apparent. Calcium malabsorption may occur in all forms of malabsorption and is therefore of no differential diagnostic value. Similarly, protein abnormalities, which might reflect maldigestion, malabsorption of amino acids or enteric loss, are common and of limited utility. Finally, steatorrhea occurs in every instance, with the possible exception of uncomplicated gastric insufficiency. Differential tests therefore relate to the absorption of xylose, vitamin B_{12}, folic acid, and iron. Practically, we can rely almost entirely on the first two, since iron absorption is indirectly tested (and iron deficiency might be due to gastrointestinal blood loss) and folic absorption parallels xylose absorption. The usefulness of the xylose and vitamin B_{12} studies in patients with steatorrhea is derived from Table 5. If both are normal, we are dealing with pancreatic or hepatobiliary disease, and other clinical findings will form the basis for the differential diagnosis. Malabsorption of B_{12} but not xylose can be caused by intrinsic factor deficiency or distal ileal pathology. Several ancillary findings can help to distinguish the two. Restoration of vitamin B_{12} absorption by exogenous intrinsic factor and the presence of achlorhydria

Table 5. *Patterns of Malabsorption*

LOCATION OF DEFECT	LIPID	XYLOSE	B_{12}	FOLATE	CA	FE	PROTEIN[a]
Extraintestinal							
gastric			+		+	+	
pancreatic	+				+[c]		+
biliary	+				+[c]		
Small intestine							
generalized	+	+	+	+	+	+	+
proximal	+	+		+	+	+	+
distal	+[b]		+		+[c]		

+Malabsorption.

[a] Pathology at almost any site may result in enteric protein loss.

[b] Steatorrhea due to either overload or bile salt deficiency.

[c] Calcium malabsorption due to vitamin D deficiency primarily.

suggest gastric disease. Hypocholesterolemia, together with the failure of intrinsic factor to correct the defect, suggests localization to the ileum. Normal B_{12} absorption with abnormal xylose tolerance localizes the pathology in the proximal small intestine, whereas abnormalities of both tests usually indicate diffuse small intestinal disease.

Etiological Diagnosis

The specific diagnosis of the basic disease follows from the interpretation of the pattern of malabsorption. Additional studies of structure and function can define gastric, pancreatic, and hepatobiliary defects. Radiological studies and intestinal biopsy can identify problems primary to the small intestine. X-ray examination should precede biopsy but may not show specific abnormalities. The classical "sprue" pattern can be seen in any generalized intestinal malabsorption. Indeed, this pattern has been observed in motility disorders not associated with malabsorption. X-ray can document the presence of strictures, fistulas, diverticula, blind loops, enteritis, visceral neuropathy, or scleroderma. Intestinal biopsy is most useful in the diagnosis of generalized or proximal intestinal pathology such as villous atrophy (compatible with non-tropical and tropical sprue), Whipple's intestinal lipodystrophy, amyloidosis and intestinal lymphangiectasia.

TREATMENT

A positive response to appropriate therapy provides final proof of diagnostic accuracy. Three therapeutic approaches are possible: (1) the treatment of the underlying disease; (2) the reversal of the pathophysiological mechanism; and (3) the replacement of nutrients by parenteral administration.

Every case of malabsorption can be treated at one of these levels. Gluten withdrawal reverses non-tropical sprue, and antibiotics are effective in Whipple's disease. Folic acid or antibiotics adequately manage tropical sprue. Replacement therapy is available for pancreatic insufficiency. Antibiotics can be used in patients with bacterial overgrowth, when the underlying dysfunction is not amenable to surgery. In cases where the inability to absorb one substrate leads to further intestinal dysfunction (methionine malabsorption, disaccharidase deficiency, glucose-galactose malabsorption, etc.) the offending substrate can be removed from the diet. Disorders associated with lipid malabsorption and enteric protein loss (intestinal lymphangiectasia, for example) may be considered in the same category, since the protein abnormalities may respond to the replacement of dietary fat with medium-chain triglyceride. In my experience the most refractory patients have been those with biliary obstruction. The absence of intraluminal bile salts causes total lipid malabsorption, but administration of exogenous bile salts is contraindicated due to their absorption in the ileum. At present we employ parenteral fat-soluble vitamins and a low-fat diet supplemented with medium chain triglyceride. For optimal therapy however, a bile salt analogue which would form micelles but would be nonabsorbable is required.

REFERENCES

1. Adibi, S. A., and Gray, S. J.: Intestinal absorption of essential amino acids in man. Gastroenterology, 52:837, 1967.
2. Booth, C. C.: Sites of absorption in the small intestine. Fed. Proc., *26*:1583, 1967.
3. Callender, S. T.: The intestinal mucosa and iron absorption. Brit. Med. Bull., 23:263, 1967.
4. Conrad, M. E., Benjamin, B. I., Williams, H. L., and Foy, A. L.: Human absorption of hemoglobin-iron. Gastroenterology, *53*:5, 1967
5. Dawson, A. M.: Absorption of fats. Brit. Med. Bull., *23*:247, 1967.
6. Dietschy, J. M.: Effect of bile salts on intermediate metabolism of the intestinal mucosa. Fed. Proc., *26*:1589, 1967.
7. Donaldson, R. M., Jr.: Role of enteric micro-organisms in malabsorption. Fed. Proc., *26*:1426, 1967.
8. Dowling, R. H.: Compensatory changes in intestinal absorption. Brit. Med. Bull., *23*:275, 1967.
9. Fisher, R. B.: Absorption of protein. Brit. Med. Bull., *23*:241, 1967.
10. Fordtran, J. S.: Speculations on the pathogenesis of diarrhea. Fed. Proc., *26*:1405, 1967.
11. Fordtran, J. S., and Dietschy, J. M.: Water and electrolyte movement in the intestine. Gastroenterology, *50*:263, 1966.
12. Gray, G. M.: Malabsorption of carbohydrate. Fed. Proc., *26*:1415, 1967.
13. Herbert, V: Megaloblastic anemia. New Eng. J. Med., *268*:368, 1963.
14. Herbert, V.: Absorption of vitamin B_{12} and folic acid. Gastroenterology, *54*:110, 1968.
15. Hofmann, A. F.: A physicochemical approach to the intraluminal phase of fat absorption. Gastroenterology, *50*:56, 1966.
16. Hofmann, A. F.: The syndrome of ileal disease and the broken enterohepatic circulation: cholerheic enteropathy. Gastroenterology, 52:752, 1967.
17. Hofmann, A. F., and Small, D. M.: Detergent properties of bile salts: correlation with physiological function. Ann. Rev. Med., *18*:333, 1967.
18. Holt, P. R.: Medium chain triglycerides. A useful adjunct in nutritional therapy. Gastroenterology, *53*:961, 1967.
19. Ingelfinger, F. J.: Regional absorption. Amer. J. Surg., *114*:388, 1967.
20. Isselbacher, K. J.: Biochemical aspects of lipid malabsorption. Fed. Proc., *26*:1420, 1967.
21. Klipstein, F. A.: Folate deficiency secondary to disease of the intestinal tract. Bull. N. Y. Acad. Med., *42*:638, 1966.
22. Lindberg, T.: Studies on intestinal dipeptidases. Acta Physiol. Scand., *69*, suppl. 285, 1966.
23. Manis, J. G., and Schachter, D.: Active transport of iron by intestine: features of the two-step mechanism. Amer. J. Physiol., *203*:73, 1962.
24. Matthews, D. M.: Absorption of water soluble vitamins. Brit. Med. Bull., *23*:258, 1967.
25. Nasset, E. S.: The role of the digestive tract in protein metabolism. Amer. J. Dig. Dis., *9*:175, 1964.
26. Newey, H.: Absorption of carbohydrates. Brit. Med. Bull., 23:236, 1967.
27. Parsons, D. S.: Salt and water absorption by the intestinal tract. Brit. Med. Bull., 23:252, 1967.
28. Senior, J. R.: Intestinal absorption of fats. J. Lipid Res., *5*:495, 1964.
29. Tobaqchali, S., and Booth, C.: Relationship of intestinal bacterial flora to absorption. Brit. Med. Bull., *23*:285, 1967.
30. Trier, J. S.: Structure of the mucosa of the small intestine as it relates to intestinal function. Fed. Proc., *26*:1391, 1967.
31. Waldman, T. A.: Protein-losing enteropathy. Gastroenterology, *50*:422, 1966.
32. Weintraub, L. R., Weinstein, M. B., Huser, H-J., and Rafal, S.: Absorption of hemoglobin iron: the role of a heme splitting substance in the intestinal mucosa. J. Clin. Invest., *47*:531, 1967.
33. Zilversmit, D. B.: Formation and transport of chylomicrons. Fed. Proc., 26:1599, 1967.

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422

Disaccharidase Deficiency

W. W. PETERNEL, M.D.*

Almost 10 years have elapsed since reports from Europe of disaccharide maldigestion[26, 27, 33, 34, 72] rekindled the interest of clinicians the world over in the digestion and absorption of these sugars. These early studies indicated that infants and children unable to digest one or more dietary disaccharides suffered from severe diarrhea and malnutrition. Subsequent reports showed a deficiency of one or more intestinal enzymes (disaccharidase) to be the cause.[4, 5, 20] During the past few years it has become apparent that intestinal disaccharidase deficiency is fairly common in both children and adults.[6, 14, 25, 32, 41] In the United States alone, more than 30 million people probably have a disaccharidase deficiency.

INTESTINAL DIGESTION AND ABSORPTION OF DISACCHARIDES

Dietary carbohydrates are chiefly disaccharides and polysaccharides. These require digestion (hydrolysis) before they can be absorbed and utilized in the body. Salivary and pancreatic amylase cleave the polysaccharide starch into the disaccharides, maltose and isomaltose. Specific enzymes (*disaccharidases*) complete the digestion of maltose, isomaltose, and the other major disaccharides of milk sugar (lactose) and cane sugar (sucrose) by splitting them into their component monosaccharides.[19, 35] Table 1 lists the major intestinal disaccharidases and the sugars they split. There are probably five different enzymes which hydrolyze maltose.[3, 63] One of these, maltase-4, also accounts for most of the sucrase-splitting activity of the intestine. Semenza et al.[3, 63] have shown the existence of a second sucrase and two intestinal lactases. Trehalase is of minor importance, since our diet contains little trehalose, the major portion coming from mushrooms and insects.

For decades biochemistry and physiology textbooks taught that disaccharidases were secreted into the intestinal lumen and there hydrolyzed the disaccharides. There was good evidence to the contrary,

---

*Assistant Professor of Medicine, University of Kentucky; University of Kentucky Medical Center, Lexington, Kentucky. Formerly Chief, Gastroenterology, Veterans Administration Hospital; Assistant Professor of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

Table 1. *Human Intestinal Disaccharidases*

ENZYME	DISACCHARIDE HYDROLYZED	% OF TOTAL ACTIVITY AGAINST EACH DISACCHARIDE
Maltase 1	Maltose	10
Maltase 2	Maltose	15
Maltase 3 (Sucrase 1)	Maltose	25
Maltase 4 (Sucrase 2)	Sucrose	100
Maltase 5	Isomaltose	100
	Maltose	50
	Palatinose	100
Lactase 1	Lactose	100
Lactase 2	Cellobiose	100
Trehalase	Trehalose	100

however, even before the turn of the century that these enzymes were located within the intestinal epithelial cells, and that enzyme activity within the intestinal lumen was due to desquamated mucosal cells.[12] Thirty-five years ago Cajori confirmed the intracellular localization of disaccharidases in dogs.[12] More recently, Miller and Crane [45, 46] showed that the isolated brush border (the most superficial luminal portion) of hamster intestinal epithelial cells contained virtually all the intestinal disaccharidase activity. About the same time, Börgstrom et al.[7] and Dahlqvist and Börgstrom[18] found that the disaccharidase activity in the lumen of the human small intestine was far too little to account for the hydrolysis of disaccharides normally absorbed, thus supporting an intracellular locus of disaccharide activity in man. Although recent histochemical studies are consistent with intracellular localization, [23] there is some evidence that the disaccharidases are actually located on the surface of the cell.[28, 29, 38, 39, 69]

Disaccharidases are present throughout the small intestine, the lowest levels occurring in the duodenum and terminal ileum.[47] Enzyme activity peaks at variable sites in the jejunum and proximal ileum. Human intestinal maltase and sucrase activity appear early in life and are fully developed before the third intrauterine month.[22] Lactase activity does not reach full activity until the end of normal gestation. Premature infants, therefore, may be transiently deficient in this enzyme.[9]

The monosaccharides formed at or just beneath the cell surface from the digestion of the disaccharides pass into the cell interior and from there into the body. The passage of any substance from the environment into cells requires a driving force which is ordinarily provided by a difference in concentration. The lipoprotein membrane of the intestinal epithelial cell, however, poses a barrier to the passage of the relatively large, water-soluble sugar molecules. Crane postulates that the sugar molecule combines with a substance in the cell membrane that permits the passage of the sugar across the lipoprotein membrane.[16] This hypothetical substance is called a carrier. The actual driving force for sugar transport is a concentration difference; thus, the process is essentially diffusion facilitated by a carrier. In addition, the intestine is

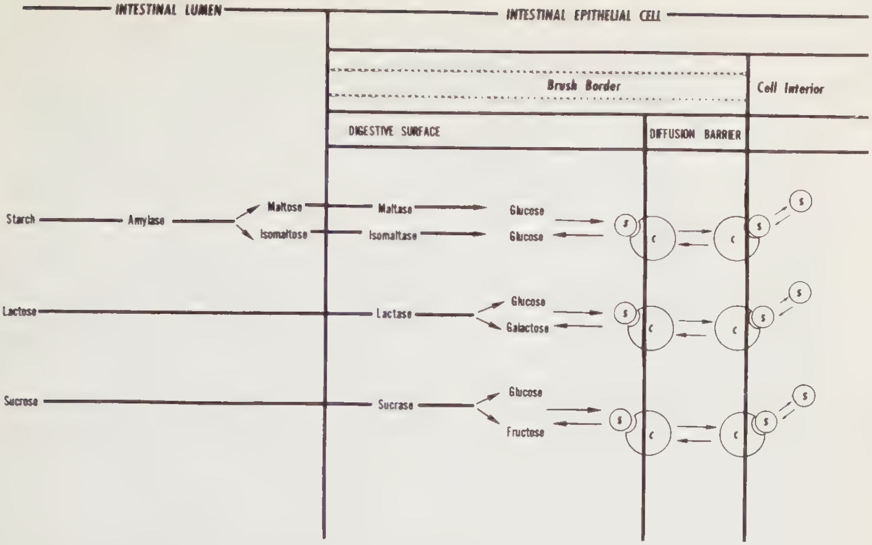

Figure 1. Intestinal digestion and absorption of disaccharides. *S*, sugar (monosaccharide); *C*, carrier.

able to transport glucose and galactose, but not fructose, against a concentration gradient; that is, glucose and galactose can be absorbed even when their concentration in the gut lumen is lower than that in the intestinal epithelial cell. This requires energy and is called active transport. Figure 1 summarizes schematically the digestion and absorption of the disaccharides. For more details the reader is referred to the reviews of Czaky[17] and Crane.[16]

CLINICAL DISORDERS ASSOCIATED WITH DISACCHARIDASE DEFICIENCY

The digestion or absorption of sugars may be impaired because of amylase deficiency in pancreatic disease, defective intestinal disaccharide hydrolysis,[20] or malabsorption of monosaccharides.[61] This re-

Table 2. *Intestinal Disorders Associated With Sugar Malabsorption*

Disaccharidase Deficiency

- Primary (inherited)
  - Lactase deficiency
  - Sucrase-isomaltase deficiency: two different enzymes are missing simultaneously
- Secondary (acquired)
  - General disaccharidase deficiency associated with intestinal disease (e.g., sprue)

Monosaccharide Malabsorption

- Primary (inherited)
  - Glucose-galactose malabsorption: glucose and galactose absorbed poorly because of a defect in the carrier; fructose is absorbed normally
- Secondary (acquired)
  - Malabsorption of all monosaccharides secondary to small intestinal disease (e.g., infection)

view is limited to abnormalities of disaccharide hydrolysis. These disorders may be primary (inherited) or secondary to associated intestinal disease (Table 2). The intestinal mucosa appears macroscopically and microscopically normal in primary deficiency states.

PRIMARY DISACCHARIDASE DEFICIENCY

Lactase Deficiency

Isolated intestinal lactase deficiency is the commonest disaccharidase deficiency in man. About 70 per cent of adult Negroes are deficient in this enzyme.[6, 11] The incidence in white adults is not as well worked out but may be on the order of 10 per cent.[6, 48]

A deficiency of intestinal lactase leads to impaired hydrolysis of lactose. The unhydrolyzed lactose exerts osmotic pressure, causing fluid to accumulate within the gut lumen. If the lactose load is sufficiently great this may lead to abdominal cramps, nausea, and diarrhea. Moreover, intestinal bacteria may ferment the undigested lactose forming organic acids. This could contribute to the diarrhea and probably explains the acid pH of the stool associated with this disorder.

SIGNS AND SYMPTOMS. The clinical manifestations associated with intestinal lactase deficiency are quite variable. Since lactose is the major sugar of breast milk, severe diarrhea usually occurs after the first few feedings in infants with congenitally deficient lactase. Dehydration, malnutrition, and electrolyte disturbances follow. If the disorder is not recognized and lactose feedings are continued, the child may die.

An adult with lactase deficiency who drinks little or no milk and has an otherwise normal intestine does not have symptoms. Those whose milk intake is greater may complain of bloating, flatulence, and crampy abdominal pains with or without diarrhea. The minimal amount of lactose necessary to produce symptoms in lactase deficient adults varies considerably, but 50 gm., the amount present in a quart of milk, ingested within a few minutes will almost invariably provoke symptoms.

DIAGNOSIS. Peroral jejunal biopsy and analysis of the specimen for lactase activity will establish the diagnosis with certainty. This assay is easily performed,[21] but is ordinarily not necessary since the lactose tolerance test correlates well with intestinal lactase activity.[20, 25, 32, 55, 71] The tolerance test is carried out as follows: after an overnight fast the patient drinks lactose (1 gm. per kg. body weight), previously dissolved in about 250 ml. of warm water and allowed to cool overnight in the refrigerator. Lemon juice may be used for flavoring. Venous blood samples are taken for glucose determination just before lactose administration and at 15, 30, 45, 60, and 90 minutes thereafter. Subjects with normal lactase activity show an elevation of blood glucose of 25 mg. per 100 ml. or more above the fasting level (Fig. 2). Elevations of blood glucose between 20 and 25 mg. per 100 ml. are borderline. Patients with lactase deficiency almost always have symptoms of bloating, abdominal cramps, or diarrhea during or shortly following the test.

Factors other than intestinal lactase activity may influence the results of the lactose tolerance test. Delayed gastric emptying will give a flat curve even in normal subjects, whereas patients with diabetes may have a normal or elevated blood sugar curve even with a lactase deficit. The use of capillary instead of venous blood will virtually eliminate falsely flat blood sugar curves,[75] but it may miss many patients with lactase deficiency.[13] A flat curve using venous blood samples associated with intestinal symptoms is highly indicative of intestinal lactase deficiency. An abnormal lactose tolerance test may be defined, therefore, as a failure of the venous blood sugar to rise more than 20 mg. per 100 ml. above the fasting value associated with symptoms of bloating, flatulence, crampy abdominal pain, or diarrhea. A flat curve and no symptoms is not diagnostically reliable and may mean delayed gastric emptying. The test should be repeated. If the repeat test does not settle the matter, analysis of the intestinal mucosa for lactase activity will.

An abnormal lactose tolerance test does not distinguish between primary and secondary lactase deficiency. An abnormal test should be followed by a glucose-galactose tolerance test to check absorption of the component monosaccharides of lactose, and a *d*-xylose absorption test as a general measure of small intestinal integrity. The glucose-galactose tolerance test is done in the same manner as the lactose test, but 0.5 gm. of glucose and 0.5 gm. of galactose per kilogram of body weight are substituted for lactose.

Several investigators have found roentgenologic study to be a valuable screening aid.[31, 40, 60] When lactase-deficient patients ingest barium sulfate mixed with lactose the unhydrolyzed sugar remains in the bowel lumen, causing an accumulation of fluid. This leads to dilution of the barium, rapid intestinal motility, and dilatation of the bowel, producing a characteristic roentgenographic picture. This technique appears promising but needs further evaluation.

ETIOLOGY. Possible causes of primary lactase deficiency are an adaptation to decreased milk intake after childhood, an inherited trait

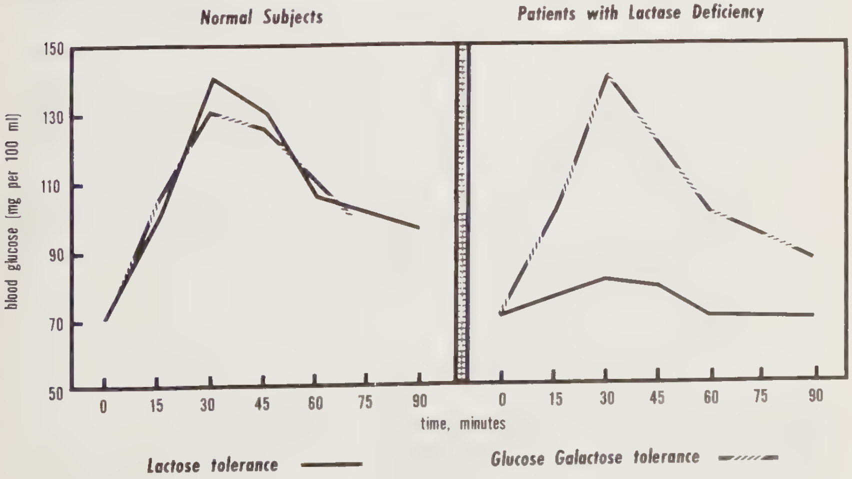

Figure 2. Oral carbohydrate tolerance tests in normal subjects compared with lactase-deficient patients.

with delayed clinical expression, or an acquired defect following intestinal injury. The excellent studies of the Johns Hopkins group support a genetic etiology.[6] They found a 70 per cent incidence of lactase deficiency in Negro adults in contrast to 10 per cent in white adults. Moreover, the incidence in Negro children increased linearly with age, from zero in five children under 6 years old to 100 per cent in 10 subjects over 24 years of age. The majority (70 per cent) of the children with lactase deficiency gave a family history of milk intolerance.

TREATMENT. Reduced intake of milk and unfermented milk products ordinarily suffices for adults. Fermented cheese, yogurt, and buttermilk do not contain lactose. Infants must be placed on a lactose-free formula such as Nutramigen. Interestingly, as they become older some may be able to drink average amounts of milk without symptoms. Not all cases of milk intolerance are due to lactase deficiency, as allergy to milk protein may be a factor.[70] Treatment, however, is similar.

Sucrase-Isomaltase Deficiency

Intestinal sucrase deficiency is uncommon but has been reported in children and adults.[57] Sucrase deficiency is always associated with isomaltase deficiency. This disorder appears to be transmitted by a single genetic factor controlling both enzymes.[62] Patients manifest an intolerance to food rich in cane sugar; symptoms are similar to those associated with lactase deficiency. Since sucrase and isomaltase account for about 75 per cent of intestinal mucosal maltase activity, intolerance to starchy foods is common. Inability to digest isomaltose, however, probably is clinically insignificant, since an average dietary intake of 135 gm. of starch a day would lead to the formation of only 4 or 5 grams of isomaltose.

Sucrase deficiency is diagnosed by the sucrose tolerance test, carried out in the same manner as the lactose tolerance test. The interpretation is identical. Management consists of placing the patient on a sucrose (cane sugar) free diet and restricting starch intake. As children with this disorder grow older they may be able to tolerate sucrose.

Maltase Deficiency

Primary intestinal maltose intolerance has not been reported. This is not surprising, since there are five different enzymes in the intestinal mucosa able to split maltose. Patients with sucrase isomaltase deficiency may have a mild starch intolerance, since starch is the major dietary source of maltose and sucrase and isomaltase provides 75 per cent of the intestinal maltose hydrolyzing activity.

SECONDARY DISACCHARIDASE DEFICIENCY

Celiac Disease (Nontropical Sprue) and Tropical Sprue

The damaged intestinal mucosa of celiac disease, in general, has less enzymatic activity than normal.[52, 61] Plotkin and Isselbacher found that all the disaccharidases were low in adults with untreated celiac disease, lactase being the most severely depressed.[59] As the mucosa improves following treatment with a gluten-free diet, the disaccharidases return toward normal. Lactase activity returns last or incompletely. These observations have therapeutic implications. Some patients with celiac disease may not improve until both lactose and sucrose are excluded from the diet.[2, 59] Acutely ill patients should probably be treated with a low-lactose, low-sucrose, gluten-free diet. These sugars may be tolerated after a few months of successful treatment, reintroduction being determined by trial. Patients with tropical sprue have a comparable impaired ability to hydrolyze disaccharides.[21, 30] A lactose-free diet might hasten the response to folic acid and antibiotics.

Kwashiorkor

Diarrhea is a common feature of kwashiorkor, and pathologic agents usually cannot be isolated. Lastose intolerance and general disaccharidase deficiency reported in the disorder[10, 15, 65] may contribute to the diarrhea. Following treatment, maltase and sucrase activities return to normal. Lactase, however, remains low.[15] In Baganda children lactase deficit may have a genetic basis as well.

Infectious Diarrhea

Pediatricians have long recognized the benefits of excluding milk from the diet of infants suffering from acute infectious diarrhea. Recently, several reports of transient malabsorption and disaccharide intolerance associated with infectious diarrhea have appeared.[50, 73] The studies of Torres-Pinedo et al.[67, 68] have clearly shown that the increased losses of water and organic acids in stool after the ingestion of milk during acute infectious diarrhea of infancy are related to impaired absorption of carbohydrates. These abnormalities reversed shortly after milk intake was stopped and intravenous therapy started. Reintroduction of milk after a few days again resulted in diarrhea. A single oral dose of the disaccharides sucrose or lactose, or even the monosaccharides glucose or fructose, provoked similar changes in stool volume and composition. In vivo jejunal profusion studies confirmed the impaired glucose absorption in these infants with acute infectious diarrhea. It seems reasonable to assume that alterations in the intestinal mucosa in infectious diarrhea are responsible for the associated sugar intolerance.

Ulcerative Colitis and Regional Enteritis

In 1925 Andersen implicated milk intolerance or allergy in the etiology of ulcerative colitis.[1] An associated intestinal lactase deficiency in these patients probably accounts for many instances of milk intolerance. Since lactase deficiency is relatively common, one might expect to find it coincidentally in some patients with ulcerative colitis. Cady et al.[11] found a 45 per cent incidence of lactase deficit among 30 white and two Negro patients with ulcerative colitis, in contrast to a 19.4 per cent incidence in 93 white control subjects. Newcomer and McGill,[49] however, reported a similar incidence (8.3 per cent) in 24 white patients with ulcerative colitis as in 100 healthy subjects (6.0 per cent). The reason for the discrepancies between these two studies is not apparent, but it could reflect genetic differences in the populations studied. For example, many Greek Cypriots suffer from milk intolerance, and 15 of 17 had flat lactose tolerance tests.[14] Disaccharidase analysis of histologically normal jejunal biopsy specimens revealed a primary lactase deficiency in 9 of 11 patients of Italian extraction in contrast to only 8 of 49 patients of Northern European descent.[56] In future studies of intestinal disaccharidases, it may be wise to include the patient's nationality as well as his race.

It would seem prudent to restrict lactose from the diet of acutely ill patients. During remission a lactose tolerance test can be done to determine the need for continued lactose restriction. In general, the same considerations apply for the evaluation and management of possible lactose intolerance in patients with regional enteritis.[66]

Peptic Ulcer

The incidence of lactase deficit in persons with peptic ulcer is probably no higher than in the general population. A subtotal gastrectomy, however, may uncover an unsuspected primary lactase deficiency.[37] After a glass of milk is swallowed, normally about 10 ml. or 0.45 gm. of lactose enters the small intestine per minute. In the postgastrectomy state, the entire glass of milk or 11.25 gm. of lactose might rapidly pass into the small intestine. With this acute lactose load, a lactase deficit may lead to symptoms for the first time following subtotal gastrectomy. This possibility should always be considered in patients who have postgastrectomy symptoms.

Miscellaneous

A condition so prevalent as intestinal disaccharidase deficiency (lactase) is bound to masquerade as other illnesses or to occur coincidentally with them. The association with cystic fibrosis,[36] abetalipoproteinemia,[59] blind loop syndrome,[59] conovid administration,[71] viral hepatitis,[13] and the de Toni-Debre-Fanconi syndrome[51] is probably coincidental.

Disaccharidase deficiency found in some patients with rosacea may be related to the abnormal jejunal mucosa found in about one third of these patients.[54] Similar mucosal abnormalities have been described in patients with dermatitis herpetiformis, eczema, psoriasis, and ichthyosis.[42] Secondary disaccharidase deficiency may exist in many of these patients. Neomycin, a powerful protein synthesis inhibitor, may impair intestinal lactase activity by interfering with its synthesis by the mucosal cell.[53] Birge et al. found an abnormal lactose tolerance test in half of 19 patients with osteoporosis.[8] Further confirmation of this is needed. Finally a significant number of patients with the diagnosis of "irritable colon syndrome" have a lactase deficit, and their symptoms improve on a lactose-free diet.[76]

SUMMARY

The utilization of disaccharides (lactose, sucrose, and maltose) requires hydrolysis by specific enzymes (disaccharidases) located within

the small intestinal mucosal cell. If these enzymes are impaired, the disaccharides will not be digested properly. This may lead to abdominal cramps, bloating, and diarrhea.

Disaccharidase deficiency may be primary (inherited) or secondary to associated intestinal mucosal disease. Primary lactase deficiency is the most frequently encountered syndrome. About 70 per cent of adult Negroes and 10 per cent of adult whites are so affected. Primary sucrase deficiency is uncommon and primary maltase deficiency has not been reported. Diseases that damage the small intestinal mucosa, such as nontropical sprue, may be associated with a depression of all the disaccharidases, especially lactase. Moreover, some of these patients may not respond to a gluten-free diet until lactose is removed from the diet as well.

The diagnosis of intestinal disaccharidase deficiency may be made by a disaccharide tolerance test. A flat blood sugar curve and associated intestinal symptoms following the ingestion of a selected disaccharide strongly suggests a deficiency of the specific disaccharidase. Other studies are necessary to determine whether the enzyme deficiency is primary or secondary to another disease.

Treatment consists in removing the offending sugar(s) from the diet.

REFERENCES

1. Andersen, A. F. R.: Gastrointestinal manifestations of food allergy. Med. J. Rec., *122*:271, 1925.
2. Arthur, A. B., et al.: Importance of disaccharide intolerance in the treatment of coeliac disease. Lancet, *1*:172-174, 1966.
3. Auricchio, S., Semenza, G., and Rubino, A.: Multiplicity of human intestinal disaccharidases. II. Characterization of the individual maltases. Biochim. Biophys. Acta., *96*:498, 1965.
4. Auricchio, S., et al.: Intestinal glycosidase activities in congenital malabsorption of disaccharides. J. Pediat., *66*:555, 1965.
5. Auricchio, S., et al.: Isolated intestinal lactase deficiency in the adult. Lancet, 2:324-326, 1963.
6. Bayless, T. M., and Rosensweig, N. S.: A racial difference in incidence of lactase deficiency. J.A.M.A., *197*:138, 1966.
7. Börgstrom, B. A., et al.: Studies of intestinal digestion and absorption in the human. J. Clin. Invest., *36*:1521, 1957.
8. Birge, S. J., Jr., et al.: Osteoporosis, intestinal lactase deficiency and low dietary calcium intake. New Eng. J. Med., *276*:445, 1967.
9. Boellner, S. W., et al.: Impairment of intestinal hydrolysis of lactose in newborn infants. Pediatrics, 36:542, 1965.
10. Bowie, M. D., Brinkman, G. L., and Hansen, J. D. L.: Diarrhoea in protein-calorie malnutrition. Lancet, *2*:550-551, 1963.
11. Cady, A. B., et al.: Significance of lactase deficit in ulcerative colitis. J. Lab. Clin. Med., *70*:279, 1967.
12. Cajori, F. A.: The enzyme activity of dog's intestinal juice and its relation to intestinal digestion. Amer. J. Physiol., *104*:659, 1933.
13. Chalfin, D., and Holt, P. R.: Lactase deficiency in ulcerative colitis, regional enteritis and viral hepatitis. Amer. J. Digest. Dis., *12*:81, 1967.
14. Cook, G. C., and Kajubi, S. K.: Tribal incidence of lactase deficiency in Uganda. Lancet, *1*:725-730, 1966.
15. Cook, G. C., and Lee, F. D.: The jejunum after kwashiorkor. Lancet, 2:1263-1267, 1966.
16. Crane, R. K.: Hypothesis for mechanism of intestinal active transport of sugars. Fed. Proc., *21*:891, 1962.
17. Czaky, T. Z.: Intestinal absorption: Changing concepts and ideas. Gastroenterology, *47*:201, 1964.
18. Dahlqvist, A., and Börgstrom, B.: Digestion and absorption of disaccharides in man. Biochem. J., *81*:411, 1961.
19. Dahlqvist, A.: Specificity of the human intestinal disaccharidases and implications for hereditary disaccharide intolerance. J. Clin Invest., *41*:463, 1962.

20. Dahlqvist, A., et al.: Intestinal lactase deficiency and lactose intolerance in adults. Gastroenterology, *45*:488, 1963.
21. Dahlqvist, A.: Method of assay of intestinal disaccharidases. Anal Biochem., *7*:18, 1964.
22. Dahlqvist, A., and Lindberg, T.: Development of the intestinal disaccharidase and alkaline phosphatase activities in the human foetus. Clin. Sci., *30*:517, 1966.
23. Dahlqvist, A.: Localization of the small-intestinal disaccharidases. Amer. J. Clin. Nutrit., *20*:81, 1967.
24. Desai, H. G., et al.: Intestinal disaccharidases in tropical sprue. Gastroenterology, *53*:375, 1967.
25. Dunphy, J. V., et al.: Intestinal lactase deficit in adults. Gastroenterology, *49*:12, 1965.
26. Durand, P.: Lattosuria idiopatica in una paziente con diarrea eronica ed acidosi. Minerva Pediat., *10*:706, 1958.
27. Durand, P., and Lamedica, F. M.: Disaccharide intolerance. Helv. Paediat. Acta, *17*:395, 1962.
28. Eichholz, A., and Crane, R. K.: Studies on the organization of the brush border in intestinal epithelial cells. J. Cell. Biol., *26*:687, 1965.
29. Gray, G. M., and Ingelfinger, F. J.: Intestinal absorption of sucrose in man: Interrelation of hydrolysis and monosaccharide product absorption. J. Clin. Invest, *45*:388, 1966.
30. Gray, G. M., and Santiago, N. A.: Disaccharide absorption in normal and diseased human intestine. Gastroenterology, *51*:489, 1966.
31. Haemmerli, U. P., and Kistler, H.: Disaccharide malabsorption. Disease-a-Month. Chicago, Yearbook Medical Publishers, 1966.
32. Haemmerli, U. P., et al.: Acquired milk intolerance in the adult caused by lactose malabsorption due to a selective deficiency of intestinal lactase activity. Amer. J. Med., *38*:7, 1965.
33. Holzel, A., Mereu, T., and Thomson, M. L.: Severe lactose intolerance in infancy. Lancet, *2*:1346, 1962.
34. Holzel, A., Schwarz, V., and Sutcliffe, K. W.: Defective lactose absorption causing malnutrition in infancy. Lancet, *1*:1126-1128, 1959.
35. Isselbacher, K. J., and Senior, J. R.: The intestinal absorption of carbohydrates and fat. Gastroenterology, *46*:287, 1964.
36. Jones, R. H. T., and Lpool, M. B.: Disaccharide intolerance and mucoviscidosis. Lancet, *2*: 120-121, 1964.
37. Kern, F., Jr., and Struthers, J. E., Jr.: Intestinal lactase deficiency and lactose intolerance in adults. J.A.M.A., *195*:927, 1966.
38. Johnson, C. F.: Disaccharidase: Localization in hamster intestine brush borders. Science, *155*:1670, 1967.
39. Larner, J., and McNickle, C. M.: Gastrointestinal digestion of starch. I. The action of oligo-1,6-glucosidase on branched saccharides. J. Biol. Chem., *215*:723, 1955.
40. Laws, J. W., and Neale, G.: Radiological diagnosis of disaccharidase deficiency. Lancet, *2*:139, 1966.
41. Littman, A., and Hammond, J. B.: Diarrhea in adults caused by deficiency in intestinal disaccharidases. Gastroenterology, *48*:237, 1965.
42. Marks, J., Shuster, S., and Watson, A. J.: Small bowel changes in dermatitis herpetiformis, Lancet, *2*:1280-1282, 1966.
43. McGill, D. B., and Newcomer, A. D.: Comparison of venous capillary blood sample in lactose tolerance testing. Gastroenterology, *53*:371, 1967.
44. McMichael, H. B., Webb, J., and Dawson, A. M.: Jejunal disaccharidases and some observations on the cause of lactase deficiency. Brit. Med. J., *2*:1037, 1966.
45. Miller, D., and Crane, R. K.: The digestive function of the epithelium of the small intestine. I. An intracellular locus of disaccharide and sugar phosphate ester hydrolysis. Biochim. Biophys. Acta., *52*:281, 1961.
46. Miller, D., and Crane, R. K.: The digestive function of the epithelium of the small intestine. II. Localization of disaccharide hydrolysis in the isolated brush border portion of intestinal epithelial cells. Biochim. Biophys. Acta., *52*:293, 1961.
47. Newcomer, A. D., and McGill, D. B.: Distribution of disaccharidase activity in the small bowel of normal and lactase-deficient subjects. Gastroenterology, *51*:481, 1966.
48. Newcomer, A. D., and McGill, D. B.: Disaccharidase activity in the small intestine. Prevalence of lactase deficiency in 100 healthy subjects. Gastroenterology, *53*:881, 1967.
49. Newcomer, A. D., and McGill, D. B.: Incidence of lactase deficiency in ulcerative colitis. Gastroenterology, *53*:890, 1967.
50. Nordio, S., and Lemedica, G. M.: Intolerance to sucrose, maltose, isomaltose and starch. *In* Durand, P., ed.: Disorders Due to Intestinal Defective Carbohydrate Digestion and Absorption. Rome, Il Pensiero Scientifico, 1964.
51. Nordio, S., et al.: Lactase deficiency in de Toni-Debre-Fanconi syndrome. Ann. Paediat., *206*:165, 1966.
52. Padykula, H. A., et al.: A morphologic and histochemical analysis of the human jejunal epithelium in non-tropical sprue. Gastroenterology, *40*:735, 1961.

53. Paes, I. C., et al.: Intestinal lactase deficiency and saccharide malabsorption during oral neomycin administration. Gastroenterology, 53:49, 1967.
54. Paton, E., Murray, E., and Watson, W. C.: Intestinal disaccharidase activity in rosacea. Brit. Med. J., *1*:459, 1966.
55. Peternel, W. W.: Lactose tolerance in relation to intestinal lactase activity. Gastroenterology, *48*:299, 1965.
56. Peternel, W. W. Unpublished data.
57. Pink, I. J.: Diarrhoea due to sucrase and isomaltase deficiency. Gut, *8*:373, 1967.
58. Plimmer, R. H. A.: On the presence of lactase in the intestine of animals and on the adaptation of the intestine to lactose. J. Physiol., *35*:20, 1906.
59. Plotkin, G. R., and Isselbacher, K. J.: Secondary disaccharidase deficiency in adult celiac disease (non-tropical sprue) and other malabsorption states. New Eng. J. Med., *271*:1033, 1964.
60. Preger, L., and Amberg, J. R.: Sweet diarrhea-roentgen diagnosis of disaccharidase deficiency. Am. J. Roentgenol., *101*:287, 1967.
61. Schneider, A. J., Kinter, W. B., and Stirling, C. E.: Glucose-galactose malabsorption. New Eng. J. Med., *274*:305, 1966.
62. Semenza, G.: Lack of some intestinal maltases in a human disease transmitted by a single genetic factor. Biochim. Biophys. Acta, *105*:386, 1965.
63. Semenza, G., Auricchio, S., and Rubino, A.: Multiplicity of human intestinal disaccharidases. I. Chromatographic separation of maltases and of two lactases. Biochim. Biophys. Acta, *96*:487, 1965.
64. Spiro, H. M., et al.: Functional histochemistry of the small bowel mucosa in malabsorptive syndromes. Gut, 5:145, 1964.
65. Stanfield, J. P., Hutt, M. S. R., and Tunnicliffe, R.: Intestinal biopsy in kwashiorkor. Lancet, 2:519-523, 1965.
66. Struthers, J. E., Jr., Singleton, J. W., and Kern, F., Jr.: Intestinal lactase deficiency in ulcerative colitis and regional ileitis. Ann. Intern. Med., *63*:221, 1965.
67. Torres-Pinedo, R., et al.: Studies on infant diarrhea. I. A comparison of the effects of milk feeding and intravenous therapy upon the composition and volume of the stool and urine. J. Clin. Invest., *45*:469, 1966.
68. Torres-Pinedo, R., et al.: Studies on infant diarrhea. II. Absorption of glucose and net fluxes of water and sodium chloride in a segment of the jejunum. J. Clin. Invest., *45*:1916, 1966.
69. Ugolev, A. M., et al.: Location of certain disaccharides and peptides in the small intestine. Nature, *202*:808, 1964.
70. Waldmann, T. A., et al.: Allergic gastroenteropathy. New Eng. J. Med., *276*:761, 1967.
71. Watson, W. C., and Murray, D.: Lactase deficiency and jejunal atrophy associated with administration of Conovid. Lancet, 65-67, 1966.
72. Weijers, H. A., et al.: Diarrhoea caused by deficiency of sugar splitting enzymes. I. Acta Pediat., *50*:55, 1961.
73. Weijers, H. A., and van de Kamer, J. H.: Fermentative diarrhoeas. *In* Durand, P., ed.: Disorders Due to Intestinal Defective Carbohydrate Digestion and Absorption. Rome, Il Pensiero Scientifico, 1964.
74. Welsh, J. D.: On the lactose tolerance test. Gastroenterology, *51*:445, 1966.
75. Welsh, J. D., et al.: Isolated lactase deficiency. Arch. Intern. Med., *120*:261, 1967.
76. Weser, E., et al.: Lactase deficiency in patients with the "irritable-colon syndrome." New Eng. J. Med., *273*:1070, 1965.

Department of Internal Medicine
University of Kentucky Medical Center
Lexington, Kentucky 40506

Current Views on Tropical Sprue and a Comparison to Nontropical Sprue

RODRIGO MENENDEZ-CORRADA, M.D.*

Tropical sprue (TS) is a form of the idiopathic intestinal malabsorption syndrome that responds to folic acid and vitamin B_{12} or both. In this paper TS will be used to designate tropical sprue. NTS will be used to designate nontropical sprue, which is considered to be synonymous with celiac or adult celiac disease, Gee-Thaysen disease, idiopathic steatorrhea, and gluten-induced enteropathy.

HISTORICAL NOTE

The term sprue itself is the anglicized form of *sprouw*, a Dutch word for a chronic diarrhea that seems to have onomatopoietic connotations. In 1669 Vincent Ketelaer, a Dutch physician, described a disease among the Belgians that he called *sprouw*. Aphthous ulcerations of the whole gastrointestinal tract seem to have been the most conspicuous manifestations, followed by "a most pernicious diarrhea."[84] In 1759 Hillary described essentially the same disorder, although in a more detailed fashion; he became acquainted with it in Barbados (B.W.I.) and believed the disease was indigenous to the tropics. Hence Hillary, not Ketelaer, is credited with the first description of TS.[19, 84] Nevertheless it was the Dutch name, not the Englishman's *aphthoides chronica*, that stuck to TS, apparently after a colonial Dutch physician (Van der Burgh) and another Englishman (Sir Patrick Manson) simultaneously described the disease in the East in 1880.[57] The recognition and description of TS thus precedes that of celiac disease (Gee, 1888) and adult celiac disease or nontropical sprue (NTS) (Gee-Thaysen disease, 1888-1932). TS was probably known to native Far Eastern physicians in even more remote epochs,[57] and nontropical sprue may have been known in classical times (Aretaeus the Cappadocian).[84] Some of the Spanish chroniclers of the conquest and colonization of America left accounts of chronic diarrheas

---

From the Medical Department, the General Medical Research Laboratory, Veterans Administration Hospital, and the University of Puerto Rico School of Medicine, San Juan, Puerto Rico

*Assistant Clinical Professor of Medicine, University of Puerto Rico Medical School; Chief, Hematology Section, and Acting Associate Chief of Staff for Research, Veterans Administration Hospital, San Juan, Puerto Rico

of the white man in the tropics that may well pass for TS. Thus the priest Abbad y Lasierra,[1] who lived in Puerto Rico between 1771 and 1776, in his history of the island published in Spain in 1782 writes: "The Spaniards who arrive in this Island, suffocated by the heat, experience great loss of appetite since due to the excessive perspiration there is lack of sufficient heat in the stomach for digestion: which results in corruption of the food [in the stomach] before it is actuated upon; most of them suffer from bothersome diarrheas that take the life of many." He goes on to recommend such "native" remedies as spices and rum "used with prudent moderation."

RELEVANCE OF TROPICAL SPRUE TO MODERN MEDICINE

Although western medicine has been acquainted with TS both in the Oriental and American tropics for over 200 years sprue still remains a disease of unknown etiology. Fortunately its therapy can be pronounced satisfactory since the year 1944 when folic acid made its appearance.[132] Before the times of folic acid there was considerable mortality from TS and before the times of liver therapy a fatal termination was likely for those who contracted the disease and remained in the tropics.[87, 131] Ashford in Puerto Rico in the first third of the century dealt with thousands of cases of TS; nowadays the island is twice as populous, but the largest health centers do not seem to be able to collect more than a few hundred cases in 10 years.[102, 111, 131] Yet, to judge by our own figures, no rapid decline in the incidence is apparent: new cases appear every year despite affluence, improved nutrition, high hygienic standards and extensive use of vitamin pills containing folic acid and vitamin B_{12} or both (Fig. 1). TS is not a common disease even in endemic areas and satisfactory, though perhaps not curative, treatment is available (certainly, no one should die from TS), yet to judge by the copious literature there is a vivid interest in it. The importance of TS as subject of scientific inquiry transcends its lack of stature as a public health problem. It is no mere word play to say that it is one of the absorbing problems of malabsorption. An eloquent example is the time and talent, not to mention the money, that the U.S. Army Sprue Team spent on this problem between 1953 and 1957. One result was the conferences on intestinal malabsorption and allied hematological problems that lasted until 1964 in San Juan. The list of the participants in these activities resembles a who's who of gastroenterology and hematology of the English-speaking world.[25] The riddle of TS, as it has been called,[15] constitutes a challenge to the scientific community and the whole field of intestinal absorption has benefited by the continued interest in it. Finally, the current conflict in Vietnam has taken American servicemen and civilians to Southeast Asia, one of the regions of endemic TS, where many have contracted it. Moreover, in several of them the disease has not become manifest until the victims were back in the U.S.A.[124, 125] In fact, ever since the times of Manson-Bahr it has been recognized that TS can remain latent as long as 20 years after return from the tropics to a temperate climate before the commencement of symptoms.[87, 88] The corollary is that TS should be

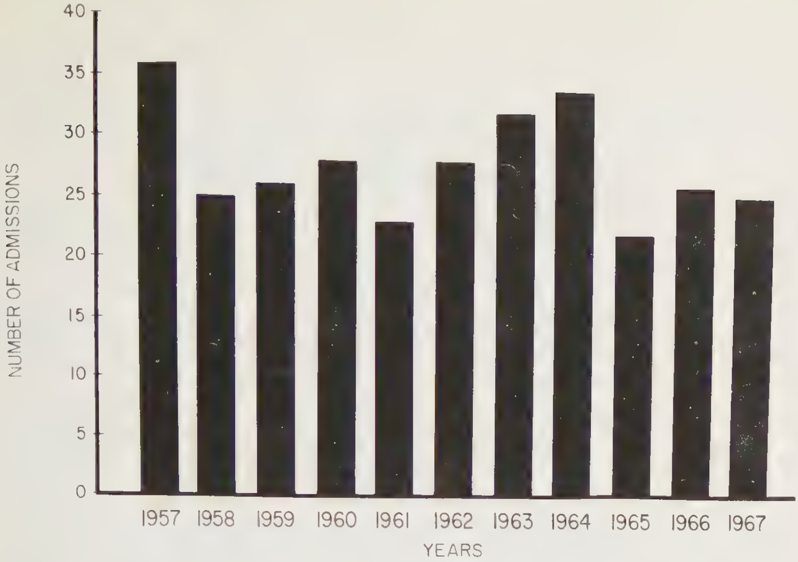

Figure 1. Annual admissions of patients with new cases of tropical sprue to the Veterans Administration Hospital, San Juan, 1957-1967.

suspected in any person who develops diarrhea after even a short sojourn in the tropics, and even if the onset occurs back home years later. The problem of the differential diagnosis with nontropical sprue is of practical importance in the northern countries, where this other type of sprue is endemic, for the management of the two diseases has fundamental differences and the prognosis for TS is much more favorable.

THE CLINICAL PICTURE OF TROPICAL SPRUE

Contemporary TS no longer presents the fervid ulcerative stomatitis that Ketelaer and Hillary described. Manson-Bahr,[87, 88] whose experience with TS in the Oriental tropics extends through half a century, described aphthous ulcerations in 22.5 per cent of his cases. In the American tropics the incidence is about the same or even less. TS as we have known it is described in Table 1. Most of the data refers to typical TS, but some observations refer to idiopathic malabsorption entities that some purists will not regard as the real TS.

Analysis of Table 1 permits us to determine which are the common signs and symptoms of TS (those with an incidence above 60 per cent). These characteristic features are insidious onset with lassitude and weakness, diarrhea (steatorrhea), loss of weight, glossitis, macrocytic anemia, hyperpigmentation of the skin, x-ray abnormalities of the small intestine, and a dramatic response to therapy with folic acid or vitamin B_{12} or both. This constellation of clinical features should make the diagnosis of TS a certainty, whether one is in Puerto Rico or Scandinavia.

But what constitute the minimal diagnostic criteria for TS? We believe that the essential conditions are contained in our definition of TS at

Table 1. *A Summary of the Clinical Features of Tropical Sprue*

		REFERENCES
Type of onset	Insidious. Average duration of symptoms about 4 months. Gastrointestinal disturbances and intermittent diarrhea for 1 year in ⅓ of patients. Occasionally explosive onset.	56, 68, 102, 111, 141
Lassitude and weakness	Common in all series. Described as the earliest symptom in India and in "military sprue" in Puerto Rico and Hong Kong.	56, 68, 99
Anorexia	Together with dyspepsia, a common late manifestation.	56, 68
Loss of weight	Incidence range 62 to 100 per cent in all series. May be extreme (50 pounds or more). Greater in those with steatorrhea in early sprue.	56, 68, 99, 102, 111
Diarrhea	Range 60 to 100 per cent in all series. Liquid or semiliquid, bulky, foul, light colored stools. Associated with pain in about ⅓ of cases. Two to 10 stools daily. Related to ingestion of food.	56, 68, 102, 111, 130, 141
Steatorrea	The rule in most reported series except one from India where 50 per cent are said to be steatorrhea-free. Associated with malabsorption of vitamin B_{12}.	27, 28, 53, 56
Glossitis	Range 60 to 94 per cent if illness is of long duration.	56, 68, 99, 102, 111
Nausea and vomiting, flatulence	Incidence about 17 per cent in the series where it is reported.	56, 68, 99, 111
Aphthae, stomatitis, ulcerations	A characteristic finding in early reports of sprue – 22.5 per cent in Manson-Bahr series in India. In other series, range 16 to 94 per cent.	68, 111, 124
Alcohol intolerance	Claimed by Ashford and Gardner to occur in American Continentals who develop sprue in Puerto Rico.	56
Anemia	Absent in "military" or other incomplete forms of sprue. Incidence in full-blown sprue is nearly 100 per cent. Rarely dimorphic, usually megaloblastic.	56, 68, 99, 119
Skin changes	Pallor and hyperpigmentation. Order of appearance: forehead, cheeks, forearms, neck, legs, and abdomen. Dry, parchment-like, scaly skin in 63 per cent. Not mentioned in early sprue.	56, 68, 111
Hemorrhagic manifestations	Extremely rare in tropical sprue. Gardner claims moderate prothrombin depletion is a late manifestation.	53, 56, 68, 102, 111, 131
Neurologic manifestations	Ten per cent in one series from Puerto Rico. Diminished or absent deep tendon reflexes and vibratory sensation in the legs. Spinal cord degeneration reported as a complication of folic acid therapy.	30, 53, 56, 68, 102, 111, 119, 130, 131
Tetany, osteoporoses, osteomalacia	Extremely rare. Blood calcium values between 8.5 and 9 mg. per 100 ml. reported in one series. Two cases with tetany have been reported.	56, 68, 111
Edema	Incidence as high as 40 per cent in one series – only in the ankles. Majority agree that edema of the ankles appears mostly in response to therapy.	68, 102, 111, 131
Small intestinal x-ray studies	Abnormalities very common but not diagnostic. More frequent abnormalities are thickening of the folds, dilatation, segmentation, and flocculation of barium.	53, 56, 68, 99

Table 1. *A Summary of the Clinical Features of Tropical Sprue. (Continued)*

		REFERENCES
Response to gluten-free diet	The best study shows that there is gradual benefit though steatorrhea does not disappear completely. Reintroduction of gluten not attended by dramatic relapse.	5, 16, 28, 68, 110
Response to folic acid and vitamin B_{12}	A diagnostic feature of tropical sprue. Lack of improvement with appropriate dosage virtually eliminates the diagnosis. In long-standing cases improvement is only partial.	56, 99, 102, 119, 124, 132, 141
Response to antibiotics	Most cases of tropical sprue respond though not so rapidly and dramatically as to folic acid. Conditioned to folate repletion. Combined folic acid-antibiotic therapy possibly the best for chronic cases.	50, 51, 57, 68, 72, 74, 99, 141
Response to medium chain triglycerides	Steatorrhea decreases, appetite returns, weight and serum lipids increase. Hematologic improvement less constant.	27
Mortality	Practically nil at present.	130, 131

the beginning of this paper – namely that there should be malabsorption, it should be primary (of unknown cause), and it should respond to folic acid or vitamin B_{12} or both.

TS may well encompass a variety of stages ranging from preclinical, asymptomatic malabsorption to the wasting disease associated with steatorrhea and megaloblastic anemia that we see in the American tropics. The image of TS that is emerging is depicted in Table 2.

Whether the preclinical malabsorption that exists in endemic areas[2, 11, 108, 128] actually evolves into overt TS is a matter that for the moment must be left sub judice. It will probably remain so until the precise etiology of TS is discovered or until one of these asymptomatic persons is actually observed to develop typical TS. A better case can be made for the so-called military or preanemic sprue,[56, 99, 140] because of the specific response to folic acid – an attribute of typical TS. It is somewhat disconcerting to learn that the only patient who refused folic acid therapy in Gardner's series[56] recovered spontaneously in a few months. What would have happened to the rest if they had not taken folic acid?

The reluctance to accept the milder disease as genuine TS is common among the older clinicians familiar with TS in the American tropics who hardly ever see acute cases of TS without full-blown megaloblastic anemia the first time they come to consultation because of diarrhea. This is still true in our practice in the VA Hospital.[94] Many of these patients claim that the diarrhea is of recent onset, perhaps a month or weeks. It does not seem likely that a person may develop advanced vitamin B_{12} or even folic acid deficiency in less than 3 months.[60, 61, 77, 100] A more careful questioning usually reveals that gastrointestinal disturbances, especially intermittent diarrhea, have been occurring for months or even years. For human reasons the patient is apt to associate the final stubborn attack of diarrhea that takes him to the physician with something he ate at the particular date; that is the beginning of his illness for him. On the other hand if we accept the scheme of Table 2 it is

Table 2. *The Clinical Spectrum of Tropical Sprue: Tentative Classification*

		REFERENCES
Preclinical tropical sprue? (latent, cryptic, submerged)	1. Asymptomatic persons with low cholesterol blood levels, low *d*-xylose absorption, minimal jejunal mucosal abnormalities (Robins et al.).	75, 108
	2. Asymptomatic relatives of tropical sprue patients with abnormal serum folate levels (Acosta-Matienzo et al.)	2
	3. Asymptomatic natives of Southeast Asia with abnormal jejunal biopsies, *d*-xylose absorption (Sprinz et al.).	128
Hill diarrhea (Manson-Bahr), military sprue (Gardner), tropical malabsorption syndrome (Jeejeebhoy et al., Lindebaum et al.)(preanemic, atypical, incomplete)	Typical features: lassitude, diarrhea, loss of weight, variable degrees of steatorrhea and glossitis, no anemia. Abnormal absorption tests and jejunal biopsy. Completely reversible with folic acid therapy alone, or sometimes just by departure from the endemic region.	56, 68, 82, 87, 88
Tropical sprue	All the features of the other two plus marked steatorrhea and cachexia. Clinical evidence of multiple deficiences, particularly megaloblastic anemia and often a chronic disease only partially responsible to folic acid or vitamin B_{12}. Curable with combined antibiotic-folic acid therapy?	102, 111, 130, 131

conceivable that preclinical cases of malabsorption with borderline folic acid deficiency may be driven into megaloblastic anemia by diarrhea of a month's duration.

There are several malabsorption entities, some of them only recently described, that do not seem to fit the criteria of either TS, NTS, secondary malabsorption syndromes, or pernicious anemia. One of them is what Hindu physicians have called parasprue.[66, 67] This disease is described as endemic in the native population of southern India and it is characterized by diarrhea, soreness of the mouth, loss of weight, and hepatomegaly. The anemia is macrocytic but hypochromic, and hypoalbuminemia is prominent. The response to folic acid or vitamin B_{12} is poor, but a good response to liver extract occurs! Two other malabsorption syndromes have been recently described associated with immunoglobulin deficiencies.[34, 37, 63]

CLINICAL PATHOLOGY

The diagnosis of TS is generally considered to be established if two or more of the absorption tests are abnormal[102] and response to folic acid and vitamin B_{12} or both is obtained (see Table 5). The most important malabsorption tests are the confirmation of steatorrhea by a fat balance study, the *d*-xylose absorption test (25 gm. or 5 gm. dosage), and the absorption of radioactive vitamin B_{12} (Schilling).[25, 53] If the untreated patient is anemic, the bone marrow should be megaloblastic. The Schilling test should differentiate TS from pernicious anemia. Histamine-fast achlorhydria occurs in TS, but intrinsic factor activity is usually present. There are odd patients whose diseases defy classification, such as the one recently reported with pernicious anemia, malabsorption, and spinal cord degeneration developing while on B_{12} treatment.[22, 34, 46] X-ray studies of the small intestine should always be done, if only to rule out secondary causes of malabsorption.[26] Today no case of malabsorption is considered well studied unless a jejunal biopsy is done. Unfortunately the avalanche of reports of mild or partial villous atrophy associated with other illnesses is such as to detract from the value of this examination as a diagnostic tool.* It does not differentiate TS from NTS. It remains useful as a research tool and as a means to judge the response to therapy.

DIFFERENTIAL DIAGNOSIS

Whether tropical sprue and nontropical sprue are distinct entities is one of the controversial problems of the idiopathic malabsorption syndromes.[3, 16, 102] The question has important implications, as has already been pointed out. Tables 1, 3, 4, and 5 have been fashioned to help us make up our minds. The most important differences between the two forms of sprue may be summarized as follows:

1. Their geographic distributions differ markedly. We have never been able to establish a diagnosis of NTS in Puerto Rico.
2. The sex incidence also seems to differ. There are many more women with NTS than with TS.
3. TS may occur in an epidemic form; NTS does not.
4. Megaloblastic anemia due to folic acid and vitamin B_{12} deficiency is much more common in TS.
5. Hemorrhagic manifestations due to prothrombin deficiency are much more common in NTS.
6. Hypocalcemia with tetany and osteomalacia are likewise much more common in NTS.
7. Circulating gluten precipitins are found in about one-third of NTS patients, not at all in TS.
8. Methylmalonic acid in the urine is found more often in TS than in NTS.
9. TS responds dramatically to folic acid and vitamin B_{12}; NTS does not.
10. In turn about 75 per cent of patients with NTS respond dramatically to strict gluten withdrawal; the response in TS is less complete.
11. In NTS the disease process seems often to spare the ileum, but does not seem to do so in TS.
12. The mortality in NTS is about 10 per cent irrespective of the therapy employed; it is practically nil in TS.
13. An unusual incidence of intestinal lymphoma, particularly of the ileum, is reported in NTS but not in TS.

On the other hand, there are also some impressive similarities between the two; both show a marked preference for light-skinned people of blood Group O; both are characterized by steatorrhea and secondary enzymatic deficiencies associated with abnormalities of the intestinal mucosa; and both seem to respond to antibacterial therapy.

Judging by the tests of malabsorption alone, one would think that

(Text Continued on page 1379.)

---

*See references 11, 35, 39, 49, 69, 78, 80, 82, 90, 120, 135, and 138.

Table 3. *Epidemiologic and Endemiologic Features*

	TROPICAL SPRUE	NONTROPICAL (CELIAC) SPRUE	REFERENCES
Geographical distribution	Endemic in some tropical and subtropical regions, specially India, Pakistan, Ceylon, Vietnam, Singapore, Hong Kong, Puerto Rico, and Cuba. Onset may occur in a temperate climate after temporary stay in tropical endemic areas.	Temperate climate. Rare in the tropics. Recently reported from India.	13, 21, 68, 76, 80, 82, 95, 96, 99, 124, 125, 140, 141
Racial susceptibility	Light skinned races more susceptible. Puerto Rico series: 255 white; 68 mulattoes; 3 Negroes.	White races more susceptible. Reported in the Hindu of northern India.	56, 68, 96, 102, 111, 124, 125, 131, 140, 141
Relation to sex	Preponderance of males. Male:female ratio in seven reports 284:181	Preponderance of females. Female:male ratio in three reports 36:13.	17, 56, 68, 96, 99, 102, 111, 128, 131, 140
Age at onset	Rare in childhood. Age range 9 to 90 years. Peak incidence between third and sixth decades.	Celiac disease onset after the age of 5 years. Adult celiac disease has a peak incidence at the third decade.	17, 56, 68, 96, 102, 111, 131, 140
Familial incidence	Abnormal malabsorption tests frequent among relatives of TS patients.	History of celiac disease in other member of the family. Abnormal jejunal biopsies in 12 per cent of relatives of celiac patients.	2, 17, 83, 128
Blood group and secretor status	Predominantly Group O blood. Bayless series (Puerto Rico), 72 per cent Group O (expected frequency 53 per cent). Author's series (Puerto Rico). Group O 68 per cent, A 29 per cent, AB 9 per cent, B 0 per cent, Rh_0(D) 91 per cent. Secretors 60 per cent, nonsecretors 40 per cent.	Predominantly Group O. Secretor status?	16, 17, 70, 93
Endemic/epidemic	Epidemic and endemic in India, Burma. Endemic in western hemisphere.	Has never been reported as epidemic.	9, 10
Relation to diet	No special relation to any nutrient.	Gluten enteropathy in about 80 per cent of cases.	17, 21, 28, 39, 56, 68, 96, 104, 111, 115, 128, 140

Table 4. *Summary of the Clinical Features of Nontropical (Celiac) Sprue*

		REFERENCES
Type of onset	In 75 per cent of patients the presenting complaint is long-standing diarrhea and weight loss. Occasionally, incapacitating bone pains, hematuria, or anemia.	17
Lassitude and weakness	Incidence 75 to 100 per cent.	17, 96
Anorexia	Incidence 41 per cent.	17
Loss of weight	Incidence as a complaint 100 per cent. Evident in 57 to 75 per cent.	17, 112
Diarrhea	Incidence 85 to 97 per cent. Average duration 1½ years. Crampy in about 33 per cent. Often nocturnal. Five or six stools per day, malodorous, watery to semisolid.	17, 112, 128
Steatorrhea	Incidence 81 to 100 per cent on 100 to 150 gm. of fat per day. Range 3 to 72 gm. per day; mean 16 gm. per day.	17, 83, 91, 128
Glossitis	Incidence 13 per cent in one report.	17
Nausea, vomiting, flatulence	Incidence 38 to 60 per cent.	17, 96, 128
Stomatitis, aphthae, ulcerations	Reported in four of seven cases in India. Widespread ulcerations of the small intestine reported in fatal cases.	13
Alcohol intolerance	Not reported.	112
Anemia	Usually mild. Maximum incidence reported 50 per cent. Commonly due to folic acid and iron deficiency (24 per cent).	17, 91, 112, 128
Skin changes	Increased pigmentation reported in 41 per cent. Pallor in 47 per cent.	17
Hemorrhagic manifestations	Incidence is 26 to 31 per cent (absent in seven Hindu cases). Due to hypoprothrombinemia. Most common site of bleeding is skin.	17, 21, 112, 96
Neurologic manifestations	Paresthesias 33 per cent in one series. Emotional disturbances 16 per cent. Severe neuropathy reported in a series of 16 cases.	17, 96, 79
Tetany, osteoporosis, osteomalacia	Blood calcium <9 mg. per 100 ml. in 7 of 42 patients. Muscle cramps, tetany, positive. Trousseau sign: 2 to 38 per cent. Bone pains and tenderness: 22 per cent.	17, 91, 96, 112, 128
Edema	Serum albumin <3.5 gm. per 100 ml. in about 60 per cent. Hypoalbuminemia severe enough to produce edema in 30 per cent.	112
Small intestine x-ray studies	Abnormal in 28 of 32 patients. Most frequent abnormalities: dilated loops, segmentation and fragmentation, coarsening. Least frequent; delayed transit time and the moulage sign.	17, 128
Response to gluten-free diet	Diagnostic of gluten enteropathy (celiac disease + adult celiac disease). About 70 to 80 per cent of all cases of idiopathic steatorrhea or nontropical sprue respond. Mucosal lesion may not regress completely.	17, 39, 104, 116, 128
Response to folic acid and vitamin B_{12}	Poor response or none at all. Indicated in the presence of megaloblastic anemia.	96, 112, 126
Response to antibiotics	Early reports suggest that prolonged administration of tetracycline results in recovery from the disease.	113
Response to medium chain triglycerides	Scarcely mentioned in the literature. Favorable effect is apparent.	64, 65
Mortality	About 10 per cent. Death may be due to intractable diarrhea, complications of steroid therapy, or lymphoma.	8, 15, 17, 104, 128, 139

Table 5. *The Clinical Pathology*

	TROPICAL SPRUE	NONTROPICAL (CELIAC) SPRUE	REFERENCES
Peripheral blood	Complete disease: mean corpuscular volume 100 to 222 cubic microns, mean corpuscular hemoglobin concentration >30 per cent. Thrombocytopenia in 66 per cent. Leukopenia less common. Hypersegmented polymorphonuclears.	Severe anemia usually not a feature. When present, anemia may be macrocytic, dimorphic, or hypochromic. In one series the lowest erythrocyte count was 3.16 million, the hematocrit 19 per cent. In many reports anemia is not even mentioned.	17, 53, 68, 96, 100, 102, 111, 131, 137
Bone marrow	Megaloblastic in 72 to 100 per cent depending on stage of the disease. Iron content increased or normal.	When anemia is macrocytic bone marrow usually is megaloblastic. Iron content of marrow may be none or decreased.	3, 17. 68, 96, 99, 100, 137
Blood folate	Complete disease: serum folate <4 μg. per ml. in 100 per cent. Incomplete disease: in about 70 per cent.	Low serum and red cell folate activity is the rule.	24, 53, 56, 68, 99, 100, 119
Schilling test	Malabsorption of vitamin B_{12} in 80 to 100 per cent of cases of complete TS. In incomplete cases about 50 per cent.	Abnormal in 12 to 43 per cent.	17, 47, 68, 100, 107, 109, 128, 140
Methylmalonic acid	Present in abnormal amounts in the urine of all cases of complete TS.	Only one patient out of seven studied had abnormal amounts in the urine.	12, 94
Blood iron and iron-binding capacity	As a rule normal in both complete and incomplete TS. Hyposideremia occurs occasionally in the course of therapy with folic acid or vitamin B_{12}.	Hyposideremia in about 33 per cent of patients; plasma iron binding capacity correspondingly increased	17, 53, 56, 91, 100, 122
Erythrocyte survival	Low in 8 of 10 patients (ineffective erythropoiesis).	No data obtained.	122
Gastric analysis	Variable incidence of histamine-fast achlorhydria – 5 to 30 per cent.	Incidence of histamine-fast achlorhydria said to be similar to that of the normal population.	54, 102, 111, 131
d-Xylose absorption	Malabsorption in 100 per cent in both complete and incomplete TS.	Malabsorption in approximately 97 per cent of patients.	17, 25, 53, 55, 56, 68, 96, 102, 109, 128, 137
Vitamin A absorption	Malabsorption in 85 to 100 per cent in both complete and incomplete TS. Depressed serum carotene levels.	Findings similar to TS.	17, 55, 56, 96, 109, 137

---

*Dormandy et al., Lancet, *1*:632, 1962; Magnus et al., Amer. J. Digest. Dis., *11*:314, 1966.

LDH and isoenzymes	High blood LDH (sometimes above 10,000 units) in all TS patients with megaloblastic marrow. LD isoenzyme rise	No data obtained.	32, 33
Bacterial, viral, fungal studies	No significant difference in bacterial yields from intestinal juices and biopsies as compared to normal controls. Similar findings in viral studies. Candida spp. can be cultured from the stools in a large percentage of TS patients but are secondary invaders.	Small intestinal flora do not differ consistently from that in control groups, though yeast and lactobacilli appeared to be more common.	7, 10, 13, 29, 40, 41, 43, 50, 56, 98, 133
Alkaline phosphatase and white cell count	Of 13 TS patients, 2 had low values, 4 high values, and 7 normal values.	No data obtained.	89
Serum proteins	TS on relapse: about 66 per cent had total serum protein values below 6 gm. per 100 ml.	Low gamma M immunoglobulin levels described in untreated celiac disease (61 per cent). Plasma proteins reduced in undernourished patients	57, 63, 102
Blood calcium	Blood calcium values low enough to produce clinical manifestations are extremely rare.	Hypocalcemia in about 66 per cent, as low as 6.3 mg./100 ml. Responds to gluten-free diet.	17, 37, 56, 68, 97, 111, 112
Prothrombin time	It is claimed that low values occur in advanced TS, but not accompanied by hemorrhagic phenomena.	Low values in about 46 per cent.	17, 53, 112
Electrolytes, etc.	Impaired absorption of salt, KI. Secretion rather than absorption of water, sodium, and potassium, and decrease in pore size in the jejunum. Low serum copper.	Findings similar to TS. Hypokalemic tubular nephropathy reported as a complication.	3, 36, 48, 53, 112, 125, 143
Jejunal biopsy	Completely flat mucosa relatively rare and responds best to folic acid and vitamin B_{12}. Convolutions, leaves, and thickening of villi more frequent and less responsive. Paneth cells present.	Completely flat jejunal mucosa much more common than in TS. Morphologic changes are the same as in TS. Absence of Paneth cells reported in patients unresponsive to gluten-free diet.	13, 17, 31, 35, 39, 68, 94, 96, 104, 116, 120, 127, 128, 135, 137
Ileal biopsy	Involvement of the ileum probably a decisive factor in TS and explains the B_{12} malabsorption. Atrophic changes more marked at the lower end of the ileum.	Involvement of the ileum probably less frequent than in TS.	13, 42, 44, 60, 61, 87, 99, 114, 115, 128

Table 5. *The Clinical Pathology (Continued)*

	TROPICAL SPRUE	NONTROPICAL (CELIAC) SPRUE	REFERENCES
Intestinal enzymes	Deficient disaccharidases – probably secondary. Folate conjugase activity in succus entericus apparently within normal. Abnormal premeability to sucrose.	With the exception of alkaline phosphatase, all mucosal enzymes have been found deficient. Usually reversible with gluten withdrawal. Return to normal lipid distribution associated with return of ATPase activity.	28, 52, 69, 73, 101, 105, 118, 123, 125, 126
Circulating gluten antibodies	Absent in TS.	Circulating precipitins to gluten demonstrable in about 33 per cent of patients while on a diet containing gluten.	4, 15, 16, 58, 71, 86, 92, 137
Chromosome studies	Bone marrow preparations: giant forms, deletions, gaps, imperfect coiling, dicentric forms. All these abnormalities return to normal with therapy.	No data.	85

there is little justification for distinguishing between the two forms of sprue, yet we are able to list 13 important features in which they differ.

TREATMENT OF TROPICAL SPRUE

There are at present at least three effective drugs against TS. We shall discuss each therapeutic agent separately.

FOLIC ACID THERAPY. Response to folic acid is a diagnostic feature of TS.[23, 30, 53, 56, 103, 111, 125, 132] The usual dosage is 15 mg. three times a day orally for about 2 weeks and then a maintenance dose of 5 mg. daily "forever" (considering how long it takes to significantly deplete folic acid, a patient with TS should not stop taking folic acid for at least 4 months).[61] Subjective symptoms of improvement appear immediately: increased appetite, a sensation of well being, disappearance of the diarrhea, and weight gain. In the anemic patient the reticulocyte response starts to appear at about the sixth day and it is maximal at about the twelfth day. Hemoglobin is usually back to normal at the end of a month, and by that time the red blood cells are normocytic. The megaloblastosis disappears within hours or a few days. Swanson et al.[134] have followed the changes in the jejunal mucosa with peroral biopsies, and they appear to closely parallel the hematologic ones. The gravest abnormalities disappear rapidly, but mild to moderate ones may persist indefinitely (together with some diarrhea and malabsorption).[121] Preanemic sprue appears to be completely reversible by folic acid alone.[56, 99] Recent evidence indicates that reversibility of TS with folic acid therapy is related to both the duration of the illness and the dosage of folic acid employed.[140] If the disease is of less than 3 months' duration, it is completely reversible with doses of 50 mg. or more of folic acid per day. Patients with longer duration of illness probably require combined antimicrobial-folic acid treatment daily in order to achieve full recovery.

VITAMIN B_{12} THERAPY. The results closely parallel those with folic acid.[22, 30, 56, 103, 136] Swanson et al.[134] suggest a slightly slower recovery of the intestinal mucosa with vitamin B_{12} than with folic acid. We have not detected any significant difference in the clinical response. We usually give 30 μg. of cyanocobalamin intramuscularly daily for a week and from then on 30 μg. every 15 days or 100 μg. every 30 days. It is sound practice to give vitamin B_{12} to all TS patients. In this way one replenishes the body stores of vitamin B_{12}, a process that takes years with folic acid alone.[53, 60, 61] The neurologic complications occasionally encountered on exclusive folic acid therapy are avoided. An occasional patient shows incomplete hematologic response to folic acid. When this occurs there is usually a limiting deficiency of vitamin B_{12} or iron.[102, 106]

ANTIMICROBIAL THERAPY. Half a dozen papers have been published on this subject,[51, 57, 72, 74] the most impressive being that of Guerra et al.,[57] who treated their patients with tetracycline for 6 months. The response is less dramatic and slower than to folic acid, but at the end it seems more complete. Hematologic improvement is especially slow to start and may not be substantial after months of therapy. The usual dosage of tetracycline (some other antimicrobial drugs are probably equally effective; erythromycin is one that is not[57]) is 1 gm. orally daily for a month and then 500 mg. orally daily for 6 months. With this regimen Guerra et al. claim complete reversibility of the disease, even in long-standing cases resistant to protracted folic acid and vitamin B_{12} therapy. Klipstein[72, 74] claims that the response to antimicrobials is conditioned by folate repletion. It does seem that the logical procedure is to start the patient on combined folic acid, vitamin B_{12}, and tetracycline therapy and after a month or so to discontinue the first two and to continue the antibiotic for 6 months. It is not yet proved that patients treated with antimicrobial agents are really cured of the disease. To demonstrate this will require a follow-up of several years. Baker has reported cases of TS unresponsive to antibacterial therapy.[9]

Other Forms of Therapy

MEDIUM CHAIN TRIGLYCERIDES (MCT). Good results with this kind of therapy alone have been achieved in both acute and chronic TS.[27] Subjective improvement occurs; the steatorrhea disappears; there is gain in weight and return of normal blood lipids, but the hematologic response is inconstant. The benefit with MCT depends on its direct absorption through the portal system. The longer-chained fats need be changed to chylomicrons and to be transported from the surface epithelium to the lacteals. MCT feeding may be a valuable adjunct measure to accelerate the recovery of the patient, and there are now preparations available commercially.

GLUTEN-FREE DIET. Despite the favorable effect of this diet on TS,[14, 28] we must admit that it offers no special advantage and an important disadvantage – it is hard to enforce outside the hospital.

CORTICOSTEROIDS AND ACTH. This form of therapy never enjoyed in TS the popularity that it has in NTS. It is no longer employed in TS.

ETIOLOGY OF TROPICAL SPRUE

A succession of theories about the etiology of TS have had their day and then passed into oblivion. Among the defunct we must list the propositions (1) that TS is due to infection by the fungi Candida spp. (Psiloses);[7] (2) that TS is a primary nutritional deficiency due to inadequate alimentation;[87, 117] (3) that the primary cause of TS is an abnormal intestinal mucosal flora;[50, 87, 88] and (4) that the cause is a blood dyscrasia.[130, 131]

The now established response to antibacterial therapy suggests a reexamination of the question of a bacterial etiology. Gaining support is the possibility of an infectious agent (a virus endemic to the tropics?) interplaying with racial or inherited susceptibilities. The observation has also been made[92] that some of the differences between TS and NTS can be explained on the basis of the localization of the bulk of the intestinal pathology, the disease process in NTS manifesting a tendency to spare the ileum.[124, 129] The ileum is the site of vitamin B_{12} absorption[47, 60, 143] and of the reabsorption of bile salts[44] – and perhaps also of the entrance to the body of antigenically active half-digested food particles descending from the diseased jejunum.

REFERENCES

1. Abbad y Lasierra, I.: Historia Geográfica, Civil y Natural de la Isla de San Juan de Puerto Rico. San Juan, University of Puerto Rico, 1959.
2. Acosta-Matienzo, J., Coll-González G., Cintrón-Rivera, A. A.: Serum folate levels in relatives of patients with tropical sprue. Clin.Res., *14*:290, 1966.
3. Adlersberg, D.: The Malabsorption Syndrome. New York, Grune and Stratton, 1957.
4. Alarcón-Segovia, D., Herskovic, T., Walcin, K. G., Green, R. A., and Scudmore, H. H.: Presence of circulating antibodies to gluten and milk fractions in patients with non-tropical sprue. Amer. J. Med., 36:485, 1964.
5. Asenjo, C. F., Rodríguez-Molina, R., Cancio, M., and Bernabe-Prida, R.: Influence of very low-fat diets with and without gluten on the endogenous fecal fat excretion of patients with tropical sprue. Amer. J. Trop. Med. Hyg., 7:347, 1958.
6. Ashford, B. K.: The etiology of sprue. Amer. J. Med. Sc., *154*:157, 1917.
7. Ashford, B. K.: The relation of Monilia psiloses to tropical sprue and an evaluation of fermentation of sugar as a criterion of specificity. Puerto Rico J. Pub. Health Trop. Med., 6:310, 1931.
8. Austad, W. I., Cornes, J. S., Gough, R. R., McCarthy, C. F., and Read, A. E. The relationship of malignant tumors of lymphoid tissue and celiac disease. Amer. J. Digest. Dis., *12*:475, 1967.
9. Baker, S. J., Mathan, V. I., and Joseph, I.: Epidemic tropical sprue. Amer. J. Digest. Dis., 7:959,1962.
10. Baker, S. J., and Mathan, V. I.: A sprue house. Amer. J. Digest. Dis., *9*:771, 1964.
11. Banwell, J. G., Hutt, M. S. R., and Tonnicliffe, R.: Observations on jejunal biopsies in Ugandian Africans. Afr. Med. J., *41*:46, 1964.
12. Barnes, L. A.: Vitamin B_{12} deficiency with emphasis on methylmalonic acid as a diagnostic aid. Amer. J. Clin. Nutrit., *20*:573, 1967.
13. Bayless, T. M., Kapelowitz, R. F., Shelle, W. M., Ballinger, W. F., and Hendrix, T. R.: Intestinal ulceration—a complication of celiac disease. New Eng. J. Med., 276:996, 1967.
14. Bayless, T. M.: Tropical sprue: Viral cultures of rectal swabs. Gastroenterology, *51*:32, 1966.
15. Bayless, T. M., Partin, J. S., and Partin, J. C.: Serum precipitins to milk, gluten and rice in tropical sprue. Johns Hopkins Med. J., *120*:310, 1967.
16. Bayless, T. M.: Tropical sprue: A comparison with celiac disease. Amer. J. Digest. Dis., *9*:779, 1964.
17. Benson, G. D., Kowlessar, O. D., and Sleisenger, M. H.: Adult celiac disease with emphasis upon response to gluten-free diet. Medicine, *43*:1, 1964.
18. Booth, C. C., and Mollin, D. L.: Chronic tropical sprue in London. Amer. J. Digest. Dis., *9*:770, 1964.
19. Booth, C. C.: The first description of tropical sprue. Gut, 5:45, 1964.
20. Booth, C. C.: Absorption from the small intestine. Sci. Basis Med. Ann. Rev., 1963, p. 173.
21. Bossak, F. T., Wang, C. I., and Adlersberg, D.: Clinical aspects of the malabsorption syndrome (idiopathic sprue). Observations in 94 patients. J. Mt. Sinai Hosp., *24*:286, 1957.
22. Brady, E. A., Estren, S., and Herbert, V.: Coexistent pernicious anemia and malabsorption in 4 patients, including one whose malabsorption disappeared with vitamin B_{12} therapy. Ann. Int. Med., *64*:1246, 1966.
23. Butterworth, C. E., Jr.: Treatment of tropical sprue. Mod. Treat., 2:320, 1965.
24. Butterworth, C. E., Jr., Nadel, H., Pérez-Santiago, E., Santini, R., and Gardner, F. H.: Folic acid absorption, excretion and leukocyte concentration in tropical sprue. J. Lab. Clin. Med., *50*:673, 1957.
25. Butterworth, C. E., Jr., Pérez-Santiago, E., Santini, R., and Martínez, J.: Studies in the oral and parenteral administration of *d* (+)-xylose. Medical Science Publication No. 5: Tropical Sprue Studies of the U.S. Army Sprue Team in Puerto Rico. Washington, Walter Reed Army Institute of Research, 1958.
26. Caldwell, W. L., Swanson, V. L., and Bayless, T. M.: The importance and reliability of the roentgenographic examination of the small bowel in patients with tropical sprue. Radiology, *84*:227, 1965.
27. Cancio, M., and Menéndez-Corrada, R.: Absorption of medium chain triglycerides in tropical sprue. Amer. J. Trop. Med. Hyg., *13*:182, 1964.
28. Cancio, M., Rodriguez-Molina, R., and Asenjo, C. F.: Gluten and tropical sprue. Amer. J. Trop. Med. Hyg., *10*:782, 1961.
29. Castellani, A., and Low, G. C.: The role played by fungi in sprue. J. Trop. Med. Hyg., *16*:33, 1913.
30. Castle, W. B.: Nutritional megaloblastic anemias. Etiologic considerations. Med. Clin. N. Amer., *50*:1245, 1966.

31. Chacko, C., Pulsons, J. G., Mather, K. S., and Baker, S. J.: Studies on villus pattern of the small intestine. J. Assoc. Physicians India, *13*:472, 1965.
32. Cintrón-Rivera, A. A., Acosta-Matienzo, J., and Díaz-Rivera, R.: Lactic acid dehydrogenase in sprue. Clin. Res. 7:262, 1959.
33. Cintrón-Rivera, A. A., Conde-del Pino, E., Maldonado, N., and Señeriz, R.: Lactic dehydrogenase isoenzymes – Clinical applications. Bol. Asoc. Med. Puerto Rico, 57:8, 1965.
34. Clark, R. R., Tonyos, R., Herbert, V., and Twonew, J. J.: Studies on two patients with concomitant pernicious anemia and immunoglubulin deficiency. Ann. Int. Med., 67:403, 1967.
35. Cooke, W. T., and Fone, D. J.: Jejunal biopsy in adult celiac disease and allied disease. Lancet, *1*:933, 1960.
36. Cooper, H., Levitan, R., Fordtran, J. J., and Ingelfinger, F. J.: Method for studying absorption of water and solute from human small intestine. Gastroenterology, *50*:1, 1966.
37. Crabbe, P. A., and Heremans, J. F.: Selective IgA deficiency with steatorrhea. A new syndrome. Amer. J. Med., *42*:319, 1967.
38. Crane, R. K.: Enzymes and malabsorption – A concept of brush border membrane disease. Gastroenterology, *50*:254, 1966.
39. Creamer, B., and Pink, I. J.: Paneth-cell deficiency. Lancet, *1*:304, 1967.
40. Cregan, J., and Hayward, N. J.: The bacterial content of the healthy human small intestine. Brit. Med. J., *1*:1356, 1964.
41. Dellipiani, A. W., and Girdwood, R. H.: The bacteriology of the small intestine in malabsorption states. Gut, 5:282, 1964.
42. Desai, H. G., Chitre, A. V., Parekh, D. V. and Jeejeebhoy, K. N.: Intestinal disaccharidases in tropical sprue. Gastroenterology, *53*:375, 1967.
43. Desai, H. G., Parekh, D. V., and Jeejeebhoy, K. N.: Bacteriological study of small intestinal fluid in tropical sprue. J. Assoc. Physicians India, *14*:203, 1966.
44. Diestchy, J. M.: The role of bile salts in controlling the rate of intestinal cholesterogenesis. J. Clin. Invest., *47*:286, 1968.
45. Editorial. The riddle of tropical sprue. Lancet, 2:691, 1960.
46. Ellis, G. S., Bauer, R. I., Owen, E. E., and Laszlo, J.: Pernicious anemia and malabsorption with spinal cord degeneration developing during vitamin B_{12} treatment. Ann. Int. Med., *64*:654, 1966.
47. Fone, D. J., Cooke, W. T., Meynell, R. J., and Harris, E. L.: Co^{58}, B_{12} absorption (hepatic survey count) after gastrectomy, ileal resection and coeliac disorders. Gut., 2:218, 1961.
48. Fordtran, J. S., Locklear, T. W., and Ewton, M. F.: Water and solute movement in the small intestine of patients with sprue. J. Clin. Invest., *46*:287, 1967.
49. Foroozan, P., and Strier, J.: Mucosa of small intestine in pernicious anemia. New Eng. J. Med., 277:533, 1967,
50. Frazer, A. C.: The intestinal flora and malabsorption syndromes. Amer. J. Digest. Dis., *9*:803, 1964.
51. French, J. M., Gaddie, R., and Smith, N.M.: Tropical sprue: Study of seven cases and the response to combined chemotherapy. Quart. J. Med., 25:333, 1956.
52. Fric, P., and Lodja, Z.: Lactic dehydrogenase isoenzymes of jejunal enterobiopsies in nontropical sprue. Clin. Chim. Acta, *12*:11, 1965.
53. Gardner, F. H.: Medical progress: Tropical sprue. New Eng. J. Med., 258:791, 835, 1958.
54. Gardner, F. H.: Observations on the cytology of gastric epithelium in tropical sprue. J. Lab. Clin. Med, 47:529, 1956.
55. Gardner, F. H., and Pérez-Santiago, E.: Oral absorption tolerance tests in tropical sprue. Arch. Int. Med., *98*:467, 1956.
56. Gardner, F. H.: A malabsorption syndrome in military personnel in Puerto Rico. Arch. Int. Med., *98*:44, 1956.
57. Guerra, R., Wheby, M. S., and Bayless, T. M.: Long term antibiotic therapy in tropical sprue. Ann. Int. Med., *63*:619, 1965.
58. Heiner, D. C., Lahey, M. E., Wilson, J. F., Gerard, S. W., Shwachwon, H. S., and Shaw, K. T.: Precipitins to antigens of wheat and cow's milk in celiac disease. J. Pediat., *61*:813, 1962.
59. Heller, P., and Venger, N.: Problems in the differentiation of the megaloblastic anemias. Med. Clin. N. Amer., *46*:121, 1962.
60. Herbert, V.: Absorption of vitamin B_{12} and folic acid. Gastroenterology, *54*:110, 1968.
61. Herbert, V.: Biochemical and hematologic lesions in folic acid deficiency. Amer. J. Clin. Nutrit., *20*:562, 1967.
62. Herbert, V., and Shapiro, S. R.: Site of absorption of folic acid in the rat in vitro. Fed. Proc., *37*:260, 1962.
63. Hobbs, J. R., and Hepner, G. W.: Deficiency of γM-globulin in coeliac disease. Lancet, *1*:217, 1968.
64. Holt, P. R.: Medium chain triglycerides – a useful adjunct in nutritional therapy. Gastroenterology, 53:961, 1967.

65. Holt, P. R., Hashim, S. A., and Van Itallie, T. B.: The treatment of malabsorption syndrome and exudative enteropathy with synthetic medium chain triglycerides. Amer. J. Gastroent., *43*:549, 1965.
66. Jain, S. R., and Sepaka, G. C.: Parasprue – a malabsorption syndrome. Clinical observations. Indian J. Med. Sc., *14*:861, 1960.
67. Jain, S. R., and Sepaka, G. C.: Parasprue – a malabsorption syndrome. A hematological, biochemical and therapeutic study. Indian J. Med. Sc., *15*:1, 1961.
68. Jeejeebhoy, K. N., Desai, H. G., Noronha, J. M., Antia, F. P., and Parekh, D. V.: Idiopathic tropical diarrhea with or without steatorrhea (Tropical malabsorption syndrome). Gastroenterology, *51*:333, 1966.
69. Jos, J., Frezal, J., Rey, J., and Lamy, M.: Étude histochemique de la Muqueuse dudenojejunale dans la maladie coeliaque. Pediat, Res., *1*:27, 1967.
70. Joske, R. A., and Benson, J. A., Jr.: ABO blood groups and non-tropical sprue. Gastroenterology, *34*:408, 1958.
71. Kivel, R. M., Kearns, D. H., and Liebowitz, D.: Significance of antibodies to dietary protein in the serums of patients with non-tropical sprue. New Eng. J. Med., *271*:769, 1964.
72. Klipstein, F. A., Schenk, E. A., and Samloff, I. M.: Folate repletion associated with oral tetracycline therapy in tropical sprue. Gastroenterology, *51*:317, 1966.
73. Klipstein, F. A.: Intestinal folate conjugase activity in tropical sprue. Amer. J. Clin. Nutrit., *20*:1004, 1967.
74. Klipstein, F. A.: Antibiotic therapy in tropical sprue: The role of dietary folic acid in the hematologic remission associated with oral antibiotic therapy. Ann. Int. Med., *61*:721, 1964.
75. Klipstein, F. A.: Tropical sprue: An iceberg disease? Ann. Int. Med., *66*:622, 1967.
76. Klipstein, F. A., Samloff, I. M., and Schenk, E. A.: Tropical sprue in Haiti. Ann. Int. Med., *64*:575, 1966.
77. Klipstein, F. A.: Folate deficiency secondary to disease of the intestinal tract. Bull. N.Y. Acad. Med., *42*:638, 1966.
78. Laster, L., and Ingelfinger, J.: Intestinal absorption aspects of structure, function and disease of the small intestine mucosa. New Eng. J. Med., *264*:1246, 1961.
79. Leading article. Adult coeliac disease and neuropathy. Lancet, *1*:664, 1967.
80. Leading article. Structure and function in idiopathic steatorrhea. Lancet, 2:873, 1967.
81. Lima-Gómez, O., Wuani, H., and Beker, S.: Tropical sprue in Venezuela (11 cases). Arch. Venez. Pat. Trop., *3*:1, 1959.
82. Lindenbaum, J., Kent. T., and Sprinz, H.: Malabsorption and jejunitis in American Peace Corps volunteers in Pakistan. Ann. Int. Med., *65*:1201, 1966.
83. MacDonald, W. C., Dobbins, W. O., and Rubin, C. E.: Studies on the familial nature of celiac sprue using biopsy of the small intestine. New Eng. J. Med., 272:448, 1965.
84. Major, R. H.: Classic Description of Disease. 3rd ed. Springfield, Ill., Charles C Thomas, 1945.
85. Maldonado, M., Seijo, A., and Rodríguez, J.: Chromosome studies in clinical practice. Bol. Asoc. Med. Puerto Rico, *59*:397, 1967.
86. Malik, G. B., Watson, W. C., Murray, D., and Cruishank, B.: Immunofluorescent antibody studies in idiopathic steatorrhea. Lancet, *1*:1127, 1964.
87. Manson-Bahr, P.: The Dysenteric Disorders. Baltimore, Williams and Wilkins Co., 1939.
88. Manson-Bahr, P.: Manson's Tropical Diseases. 16th ed., Baltimore, Williams and Wilkins Co., 1966.
89. Martínez-Maldonado, M., Menéndez-Corrada, R., and Rivera de Sala, A.: Diagnostic value of alkaline phosphatase in leukocytes. Amer. J. Med. Sc., *248*:175, 1964.
90. Mayoral, L. G., Tripathy, K., García, F. T., Klahr, S., Bolaños, O., and Chitis, J.: Malabsorption in the tropics: A second look. I. The role of protein malnutrition. J. Clin. Nutrit., *12*:8, 1967.
91. McGuigan, J. E., and Wolwiler, W.: Celiac sprue – malabsorption of iron in the absence of steatorrhea. Gastroenterology, *47*:636, 1964.
92. Menéndez-Corrada, R., and Belaval, M. E.: Gluten antibodies and tropical sprue. Amer. J. Digest. Dis. (in press).
93. Menéndez-Corrada, R., and Aymerich, S.: ABO Rh_0(D) blood groups and secretor status of tropical sprue patients. Bol. Asoc. Med. Puerto Rico (in press).
94. Menéndez-Corrada, R.: Unpublished observations.
95. Milanes, F.: Changes in the epidemiology and clinical behavior of sprue occurring in Cuba during the 3 decades 1927 1957. Arch. Hosp. Univ. (Havana), *12*:125, 1960.
96. Misra, R. S., Kasthuri, D., and Chuttan, H. R.: Adult coeliac disease in the tropics. Brit. Med. J., 2:1230, 1966.
97. Moss, A. J., Waterhouse, C., and Terry, R.: Gluten sensitive enteropathy with osteomalacia, but without steatorrhea. New Eng. J. Med., 272:823, 1965.
98. Nadel, H., and Gardner, F. H.: Bacteriological assay of small bowel secretion in tropical sprue. Amer. J. Trop. Med. Hyg., *5*:686, 1956.
99. O'Brien, W. O., and England, M. W.: Military tropical sprue from Southeast Asia. Brit. Med. J., 2:1157, 1966.

100. O'Brien, W. O., and England, M. W.: Folate deficiency in acute tropical sprue. Brit. Med. J., 2:1573, 1964.
101. Padykula, H. A., Straus, E. A., Ladman, A. J., and Gardner, F. H.: A morphologic and histochemical analysis of the human jejunal epithelium in non-tropical sprue. Gastroenterology, *40*:735, 1961.
102. Pérez-Santiago, E., and Butterworth, C. E., Jr.: Definitions and diagnosis of sprue. Amer. J. Digest. Dis., 2:225, 1957.
103. Pérez-Santiago, E., Sheehy, T. W., Rubin, M., Haddock, G., and Fradera, J. V.: Combined folic acid – vitamin B_{12} deficiency in tropical sprue. Proceedings of conference on tropical anemia and intestinal malabsorption, San Juan, April 1960.
104. Pink, I. J., and Creamer, B.: Response to a gluten-free diet of patients with the coeliac syndrome. Lancet, *1*:300, 1967.
105. Plotkin, G. R., and Isselbacher, K. L.: Secondary disaccharidase deficiency in adult celic disease and other malabsorption states. New Eng. J. Med., *271*:1033, 1964.
106. Rivera, J. V., Rodríguez de la Obra, F., Martínez-Maldonado, M., and Fernández, A.: Anemia due to vitamin B_{12} deficiency after treatment with folic acid in tropical sprue. Amer. J. Clin. Nutrit., *18*:110, 1966.
107. Rivera, J. V., and Bernabe-Prida, R.: Absorption of vitamin B_{12} in tropical sprue. Amer. J. Trop. Med. Hyg., *11*:718, 1962.
108. Robins, S. J., García-Palmieri, M., and Rubio, C.: Low serum cholesterol levels and subclinical malabsorption. Ann. Int. Med., *66*:556, 1967.
109. Rodríguez-Rosado, A. L., and Sheehy, T. W.: The role of calcium on the intestinal absorption of vitamin B_{12} in tropical sprue. Amer. J. Med. Sc. 242:548, 1961.
110. Rodríguez-Molina, R., Asenjo, C. F., and Cancio, M.: Steatorrhea in tropical sprue patients in Puerto Rico. Amer. J. Trop. Med. Hyg., *6*:780, 1957.
111. Rodríguex-Molina, R.: Fundeamental concepts in the diagnoses of sprue. Ann. Int. Med., *40*:33, 1954.
112. Ross. J. R., Gibb, S. P., Hoffman, D. E., Stefanyk, H. N., and Alvarez, S. Z.: Systemic manifestations of gluten enteropathy. MED. CLIN. N. AMER., *50*:515, 1966.
113. Roufail, W. M., and Ruffin, J. M.: Effect of antibiotic therapy on gluten sensitive enteropathy. Amer. J. Digest. Dis., *11*:587, 1966.
114. Rubin, C. E.: Malabsorption, celiac sprue. Ann. Rev. Med., *12*:39, 1961.
115. Rubin, C. E., Brandberg, L. L., Flick, A. L., Phelp, P., Parmentier, C., and Van Niel, S.: Studies of celiac sprue. III. The effect of repeated wheat instillation into proximal ileum of patients on gluten free diet. Gastroenterology, *43*:621, 1962.
116. Samloff, M., Davis, J. J., and Schenk, E. A.: A clinical and histochemical study of celiac disease before and during a gluten-free diet. Gastroenterology, *48*:155, 1965.
117. Santini, R., Berger, F. M., Bordasco, G., Sheehy, T. W., Aviles, J., and Davila, I.: Folic acid activity in Puerto Rican foods. J. Amer. Diet Assoc., *41*:562, 1962.
118. Santini, R., Martinez de Jesus, J., Butterworth, C. E., Jr., and Pérez-Santiago, E.: Evidence of increased intestinal absorption of molecular sucrose in sprue. Amer. J. Digest. Dis., 2:663, 1957.
119. Sarin, L. R., Kujar, N. M., and Mehta, S. R.: Serum B_{12} and folic acid in tropical sprue. Indian J. Med. Sci., *20*:253, 1966.
120. Schenk, E. A., Samloff, I. M., and Klipstein, F. A.: Morphologic characteristics of jejunal biopsy in celiac disease and tropical sprue. Amer. J. Path., *47*:765, 1965.
121. Sheehy, T. W., Baggs, B., Pérez-Santiago, E., and Floch, M. H.: Prognosis of tropical sprue. A study of the effect of folic acid on the intestinal aspects of acute and chronic sprue. Ann. Int. Med., 57:892, 1962.
122. Sheehy, T. W., Rubini, M. R., Bacó-Dapena, R., and Pérez-Santiago, E.: Erythrokinetics in the megaloblastic anemia of tropical sprue. Blood, *15*:761, 1960.
123. Sheehy, T. W., Cohen, W. C., Wallace, D. K., and Legters, L. L.: Tropical sprue in North Americans. J.A.M.A., *194*:1069, 1965.
124. Sheehy, T. W., Anderson, A. R., and Baggs, B. E.: Carbohydrate studies in tropical sprue. Amer. J. Digest. Dis., *11*:461, 1966.
125. Sparberg, M., Knudson, K. B., and Sanders, F.: Tropical sprue from the Philippines. Report of 3 cases. Mil. Med., *132*:809, 1967.
126. Spiro, H. M., Filipe, M. I., Stewart, J. S., Booth, C. C., and Pearse, G. E.: Functional histochemistry of the small bowel mucosa in malabsorptive syndromes. Gut, 5:145, 1964.
127. Sprinz, H.: Comments on the histopathology of sprue. Proceedings of conference on tropical anemia and intestinal malabsorption, San Juan, April 1960.
128. Sprinz, H., Sribhibhadh, R. S., Gangarosa, E. J., Benyajata, C., Kundel, D., and Halstead, S.: Biopsy of the small bowel in Thai people. Amer. J. Clin. Path., 38:43, 1962.
129. Stewart, J., Pollock, D., Hoffbrand, A., Mollin, D. L., and Booth, C. C.: A study of proximal and distal intestinal structure and absorptive function in idiopathic steatorrhea. Quart. J. Med., *36*:425, 1967.

130. Suárez, R. M.: The past, present and future of sprue in Puerto Rico. Minnesota Med., *45*: 820, 1962.
131. Suárez, R. M.: Revisión del esprú. Estudio Clínico y hematologia de 150 casos. Puerto Rico J. Pub. Health Trop. Med., *14*:176, 1938.
132. Suárez, R. M., Spies, T. D., and Suárez, R. M., Jr.: Use of folic acid in sprue. Ann. Int. Med., *26*:643, 1947.
133. Swanson, V. L., Haley, N. P., and Wheby, M. S.: Mycological study of jejunal biopsy specimens from patients with tropical sprue. Amer. J. Trop. Med. Hyg., *14*:1066, 1965.
134. Swanson, V. L., Wheby, M. S., and Bayless, T. M.: Morphologic effects of folic acid and vitamin B_{12} on the jejunal lesion of tropical sprue. Amer. J. Path., *49*:167, 1966.
135. Swanson, V. L., and Thomassen, R. W.: Pathology of the jejunal mucosa in tropical sprue. Amer. J. Path., *46*:511, 1965.
136. Tasker, P. W. G., Mollin, D. L., and Berriman, H.: Vitamin B_{12} deficiency in the megaloblastic anemias of Malaya. Brit. J. Haemat., *4*:167, 1958.
137. Taylor, K. B., Truelove, S. E., and Wright, R. J.: Serologic reaction to gluten and cow's milk proteins in gastrointestinal disease. Gastroenterology, *46*:99, 1964.
138. Townley, R. R., Cass, M. H., and Anderson, C.: Small intestinal mucosal pattern of coeliac disease and idiopathic steatorrhea seen in other situations. Gut, *5*:51, 1964.
139. Vega de Rodríguez, G., Flock, M. H., and Haddock, L.: Potassium deficiency in tropical sprue. Amer. J. Digest. Dis., *7*:968, 1962.
140. Walia, B. N. S., Sidhy, J. R., Tandon, B. N., Ghai, O.P., and Bhargava, S.: Coeliac disease in North Indian children. Brit. Med. J., *2*:1233, 1966.
141. Webb, J. F., and Simpson, B.: Tropical sprue in Hong Kong. Brit. Med. J., *2*:1162, 1966.
142. Wesser, E., Jeffries, G. H., and Sleisenger, M. H.: Progress in gastroenterology: Malabsorption. Gastroenterology, *50*:811, 1966.
143. Wilson, T. H.: Membrane transport of vitamin B_{12}. Medicine, *43*:669, 1964.

Box 10356
Caparra Heights, Puerto Rico 00922

Nonspecific Inflammatory Diseases of the Intestines

RENE A. ALBACETE, M.D.*

Chronic ulcerative colitis and regional enteritis are the most common and well recognized nonspecific inflammatory diseases of the intestine. Granulomatous colitis, on the other hand, has only recently been differentiated from chronic ulcerative colitis. To clarify the differential characteristics of these two inflammatory processes of the colon they will be described together.

CHRONIC ULCERATIVE COLITIS AND GRANULOMATOUS COLITIS

Chronic ulcerative colitis (CUC) has been studied since 1875, when William Wilks first described this nonspecific ulcerative disease of the colon. Since then, this disease has been differentiated from other specific diseases of the large bowel, such as bacillary and amebic dysenteries, lymphogranuloma venereum, and diverticulitis. From the year 1932 to the 1950's, it was considered that in the group of nonspecific inflammatory conditions of the intestines, CUC was limited to the colon and regional enteritis (RE) was localized to the small intestine. In 1951, Rappaport, Burgoyne, and Smetana,[22] as well as Wells[30] a year later, reported that RE frequently involved the large bowel. But it was in 1954 when Neuman et al.[21] and Neuman and Dockerty[20] gave an excellent clinical and pathological description of an inflammatory process of the colon dissimilar to CUC which they called "regional (segmental) colitis" and which now is known as granulomatous colitis (GC).

Since then there has been a gradual acceptance of this granulomatous process of the colon, especially by British workers, who prefer to call it "Crohn's disease of the colon." The extension of RE into the colon is also called "ileocolitis." This should be differentiated from the uncommon extension of CUC into a short segment of the ileum, which is called "backwash ileitis." In ileocolitis, the involved ileum and colon

---

* Chief, Gastrointestinal Section, Veterans Administration Hospital; Assistant Professor, Department of Internal Medicine, Howard University, Washington, D.C.

have the characteristics of RE and in backwash ileitis, the ileum has all the radiological and pathological features of CUC.

GC, even in the absence of involvement of the ileum, should be considered as the same pathological process as RE. But for the sake of clarifying its distinguishing features from those of CUC, it will be described jointly with the latter.

Pathology

The pathology of CUC is distinctly different from that of GC. In CUC the inflammatory process is limited to the mucosa and submucosa. There is little tendency to fibrosis and there is no granulomatous reaction. The process involves the rectum in almost all cases and is rarely segmental. The marked inflammatory reaction of the mucosa with richness in capillaries is expressed by the hyperemia and tendency to bleed, and the attempts at regeneration by the formation of pseudopolyps and neoplastic changes.

In GC, by contrast, the inflammatory reaction is transmural, involving all the layers of the colon and frequently presenting sarcoid-like granulomas. There is thickening and fibrosis similar to that seen in RE. The involvement of the mucosa is less striking than in CUC, lacking its richness in capillaries and hence its tendency to bleed, as well as its marked tendency toward regeneration. The ulcerations tend to be deep and longitudinal, with a cobblestone appearance of the mucosa secondary to the thickening of the submucosa. The involvement of the colon may be segmental, frequently sparing the rectum, with a tendency to fistula and stricture formation.

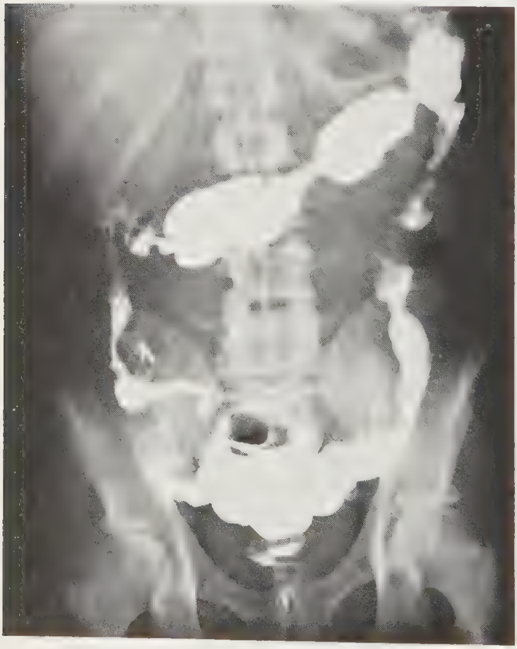

Figure 1. Granulomatous colitis with segmental involvement of the colon and associated extension of the ileum. Note the cobblestone appearance of the ascending colon. The ileum demonstrates the transmural nature of the inflammatory process. Multiple transverse fissures are noted.

The differentiation of CUC from GC is not always easy. Recently in a study of 151 cases of primary ulcerative disease of the colon by Hawk and Turnbull,[9] 16 cases could not be classified in either group. In 45 per cent of 87 cases of GC (Crohn's disease of the colon) studied by them, no granulomas were found. In these atypical cases the differentiation should be based on the clinical and radiological characteristics as well as the pathological findings. In the latter, as mentioned by Morson,[2] the findings of a transmural inflammation with fissures and abscesses would make the diagnosis of GC most likely.

Differential Clinical Manifestations

The incidence of CUC is higher than that of GC, and both conditions have a preference for the young, but it may develop at any time of life without sexual preference.

Bloody diarrhea, abdominal pain, and annoying rectal tenesmus are the outstanding clinical manifestations of CUC. In slightly more than half of the patients, the course is intermittent with episodes of activity which alternate with variable periods of remission characterized by almost normal bowel function and absence of blood in the stools. In the episodes of activity the loss of weight and strength and other extraintestinal manifestations depend on the severity of the attack. In other patients, the disease may follow a chronic continuous course. In about 18 per cent of the cases the disease may be limited to the rectosigmoid area, and in this group rectal bleeding is the most common symptom, often unaccompanied by diarrhea or systemic manifestations.[25]

In GC, diarrhea and abdominal pain are also outstanding symptoms, but here the absence of daily rectal bleeding is striking. In almost half of the cases, an isolated short episode of mild gross rectal bleeding can be elicited, usually associated with anorectal pathology. Although occasionally the diarrhea can be intermittent, GC is a less remitting disease than CUC. On physical examination, weight loss may be marked in many patients, and on abdominal examination, occasionally a tender inflammatory mass can be palpated. The latter finding is less common than in classical RE involving the ileum and unusual in CUC. In GC, anal lesions are more common than in CUC. Lockhart-Mummery and Morson,[17] in a large series of cases studied, found anal fissure, perianal and ischiorectal abscess, fistula, and ulcerations in 80 per cent of the cases, while in CUC, they found these in only 23 per cent.

Sigmoidoscopic Examination

In GC, in addition to the frequency of the anal lesions already mentioned, the rectal mucosa frequently is normal in appearance. Although the finding of a normal mucosa on sigmoidoscopy should strongly suggest GC, it should by no means rule out the possibility of CUC. Recently Korelitz,[11] in a study of 65 patients with adequate pathological study of surgical specimens and without apparent rectal involvement, found that 47 (72 per cent) had evidence of granulomatous disease and 18 had CUC. In those cases in which the clinical and radiological examinations suggest GC, biopsy of the anal lesions and even of the normal-looking rectal mucosa may be rewarded by finding a granulomatous lesion.

In those cases of GC with rectal involvement, the gross sigmoidoscopic picture may be indistinguishable from that of CUC, and only a biopsy with finding of a granulomatous lesion may be helpful. In others, the involvement may be patchy with areas of normal intervening mucosa, in contrast with the diffuseness of CUC.

Radiological Examination

In many cases of nonspecific ulcerative disease of the large bowel, the radiological features are distinctive enough to differentiate GC from CUC.[16, 32] However, not infrequently this differentiation is difficult even after a pathological study of the resected specimen has been performed. The chief roentgen diagnostic features of GC are skip areas, longitudinal ulcerations, transverse fissures, and eccentric involvement, producing pseudodiverticula-like formation and a cobblestone appearance of the mucosa. Occasionally GC may be localized to a single short segment of the colon, simulating a malignant lesion, but more commonly the short segmental areas of involvement are multiple.[6, 23] This points out the importance of an adequate barium enema and small bowel series in order to detect segmental lesions.

Involvement of the ileum also helps in the differentiation of GC from CUC. In about 10 per cent of the cases of CUC a backwash ileitis is observed. This has three characteristics: (1) continuity with the cecum; (2) less than 10 cm. of involvement; and (3) involvement is superficial, identical to that found in the colon. In GC, by contrast, the involvement of the ileum is more frequent. In almost 50 per cent of the cases variable extension in the small intestine, which is not necessarily contiguous, may exist, presenting the characteristics of RE.

The differentiation of these two ulcerative conditions of the colon depends on the presence of one or more of the radiological features described and on the clinical and biopsy findings.

Complications

The colonic complications of CUC rarely seen in GC are pseudopolyposis, toxic megacolon, and carcinoma. Recently Hawk and Turnbull[9] have reported toxic megacolon in 16 per cent of the 87 cases of GC studied by them, but other workers have not observed it.[13] The incidence of carcinoma in CUC increases with the duration of the disease, occurring in 0.7 to 12.5 per cent of all cases. In contrast, carcinoma is rare in GC, only two cases of this association, probably coincidental, having been reported in the literature. Stricture in CUC usually indicates carcinoma, while in GC it means fibrosis. Fistulous tracts and abscess when present are hallmarks of the granulomatous type. Free perforation with peritonitis, which can complicate the course of CUC in approximately 2 per cent of the cases, is very rare in GC. It seems that arthritis, skin lesions, and hepatic abnormalities, although occasionally seen in GC, are less frequent than in CUC. Even though in GC and RE granulomas may be widespread throughout the gastrointestinal tract and mesenteric nodes, granulomatous involvement of the liver has not been reported.[7]

Prognosis and Treatment

CUC must be considered a serious disease, characterized by multiple attacks and serious local and systemic complications which shorten the life span of the patient. In contrast, when the disease is limited to the rectosigmoid, it usually runs a milder course and complications are less frequent.

Experience in the treatment of CUC is extensive. For the last two decades, with the improvement of general medical measures, the advent of Azulfidine and adrenal steroids, and the recognition of the beneficial influence of supportive psychotherapy in the sense of establishing a good doctor-to-patient relationship, the course of CUC has undoubtedly been modified. Although one should rarely consider the disease as cured by medical treatment, the acute flare-ups are more easily controlled, and in the eventuality of serious complications, the patient is better prepared for total colectomy.

The accepted indications for surgery are carcinoma, intestinal obstruction, perforation, and those medically treated uncontrollable complications such as massive hemorrhage, toxic megacolon, and chronic unremitting disease. Recently described hepatobiliary complications such as pericholangitis[26] and sclerosing cholangitis[29] may be an indication for colectomy in active disease. There is some evidence that these complications may lead to biliary cirrhosis and even to biliary tract carcinoma.[27] The ideal surgical procedure is total colectomy and ileostomy.

The course of GC, on the other hand, resembles that of RE not only in respect to its complications already mentioned, but because of its resistance to medical treatment. However, it must be realized that the experience in GC is limited. This is due in part to its lower incidence, as well as to the fact that it has been only recently differentiated from CUC and fully studied only for the past decade. In my experience, Azulfidine

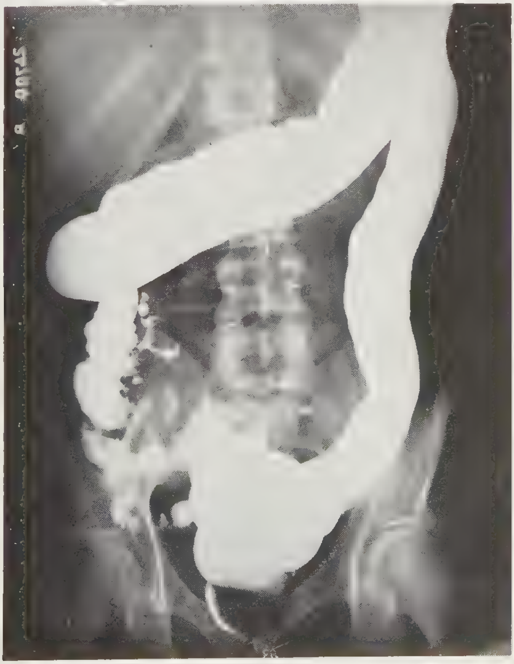

Figure 2. Granulomatous colitis, showing multiple fistulas of the ascending colon. The transverse and left colon were not involved.

has not been beneficial, and although adrenal steroids afford improvement, they are frequently unsuccessful in maintaining adequate nutrition and control of symptoms.

Because GC frequently spares the rectum, many patients are submitted to surgery, with partial colectomy and ileocolostomy. The criteria for surgical treatment of this disease have not yet been settled. While some workers[11] report fairly good results, others have observed a high incidence of recurrence, both proximal as well as distal to the anastomosis.[11] Probably the incidence of recurrence after surgery will rise with more long-term follow-up studies.

REGIONAL ENTERITIS

Thirty-five years have elapsed since Crohn, Ginzburg, and Oppenheimer[4] described regional enteritis, separating this chronic nontuberculous granulomatous process of the intestine from the specific granulomas of the gastrointestinal tract. Since then, many new aspects of the disease have become known, especially in relation to its distribution. Although the disease is commonly localized to the terminal ileum, occasionally it may present a spotty distribution throughout the gastrointestinal tract, from the stomach proximally to the rectum distally. The localization in the colon has been recently recognized and called granulomatous colitis, and the combined localization in the small and large bowel has been called ileocolitis. Its etiology is still unknown,[12] and the treatment has shifted to a medical approach unless uncontrollable complications render surgery inevitable.

With respect to its incidence, regional enteritis has a widespread geographical distribution.[3, 5] Although it is more frequent among Jews, it is found in other ethnic groups. In Negroes it seems to be less common.

With relation to ulcerative colitis, regional enteritis is less common, the proportion being 4 to 1.

Pathology

The gross appearance at laparotomy is similar, although with some variance, whether the disease is localized in the ileum, jejunum, or large bowel. The intestine appears thickened, rigid, and hoselike. The serosa appears granular, infiltrated, and covered by mesenteric fat. On microscopic examination, there is a chronic inflammatory reaction with edema and fibrosis, involving especially the mucosa, submucosa, and serosa. Granulomas are frequently seen, but they are not constant.

Clinical Manifestations

This is a disease predominantly of the young, but it can be present in all age groups and has no sexual preference. The onset of regional enteritis (RE) may be abrupt, simulating acute appendicitis or acute intestinal obstruction. In most of these cases, a careful history and physical examination demonstrates mild episodic symptoms compatible with RE. In this respect, it would be useful to perform a careful examination, looking for anorectal lesions in which biopsy finding of a sarcoid-like granuloma may help the diagnosis. This should be differentiated from the ill-defined acute inflammation of the terminal ileum called acute ileitis, which is not preceded by intestinal symptoms and is not usually followed by chronic regional enteritis.[8, 24]

Most commonly RE presents an insidious onset with bouts of flatulence, mild cramps, and diarrhea, often attributed to dietary indiscretions or functional disorders. As the disease progresses these symptoms become intensified and associated with weight loss, fever, palpable mass, and fistulas until medical advice is sought. X-ray studies confirm the diagnosis.

The pain of RE, which has been well described by Van Patter,[28] may be peristaltic in type, usually intermittent, and commonly, but not always, associated with diarrhea. A second type of pain is that of a steady constant aching of localized peritoneal irritation secondary to the serosal irritation of the involved intestine. The abrupt intensification of this type of pain may simulate an acute abdominal condition, which can be misdiagnosed if the disease has not been previously recognized or if an adequate history is not taken in this acute exacerbation.

Diarrhea, although frequent, is absent in about 10 per cent of the patients. Its severity depends on the extension of the disease in the small and large intestine. Occasionally it may be associated with steatorrhea. Fever, though infrequent, is occasionally its major manifestation. When it is present, it indicates marked activity of the disease or the presence of fistula and abscess. Physical examination may show a tender fixed mass in the right lower quadrant in about 35 per cent of the cases. Anal fistulas, fissures, and ulcers are frequently observed. A biopsy of these anorectal lesions showing noncaseating granulomas may be helpful in the differential diagnosis from chronic ulcerative colitis when there is extensive involvement of the large bowel. These anal lesions with a sarcoid-like reaction may precede the clinical and radiological manifestations for a period varying from 2 to 5 years.[2]

Among the complications, besides the anorectal lesions already mentioned, internal and external fistulas are common. Free perforation with diffuse peritonitis is rare due to the characteristically transmural inflammation in this disease. Only six cases have been reported in the literature.[18, 19] Intestinal obstruction, when present, does not necessarily indicate the need for surgical intervention. Quite often it may be due to an acute exacerbation with edema and spasm, which can be controlled with steroid therapy and tube decompression. This episode of acute intestinal obstruction must be differentiated from the advanced case of fibrotic stenosis, which requires surgery. Steatorrhea is infrequent unless there is an extensive diffuse or segmental involvement, or previous extensive resection. In the presence of steatorrhea with terminal ileitis of less than 3 feet of involvement, other skip areas should be looked for. Also the existence of some other cause of malabsorption should be investigated. Vitamin B_{12} deficiency with megaloblastic anemia should be expected in long-standing involvement of the ileum or in extensive involvement of this segment. Protein-losing enteropathy, amyloidosis, arthritis, erythema nodosum, clubbing of the fingers, personality changes, and electrolyte depletion may also occur.

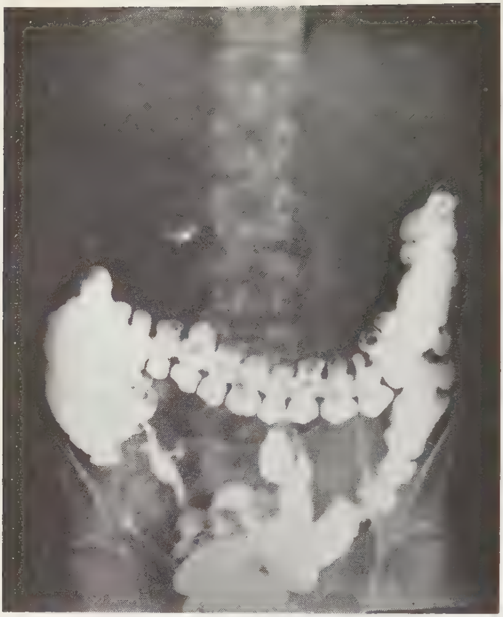

Figure 3. Regional enteritis involving the terminal ileum, showing fistula formation and narrowing.

Treatment

Three and one half decades of clinical experience with regional enteritis have shown that the primary treatment is medical, with surgical treatment performed only in the presence of complications which cannot be controlled by medical means. Although there is no specific therapeutic measure for this disease, the reason for this policy is based on the high recurrence rate after surgery, which usually is about 50 per cent.[15] Although a large number of patients will eventually require surgery, there is no proof that the recurrence rate is less or postponed as a result of early operation. On the other hand, there seems to be some indication that better surgical results may be obtained with long-standing disease or when performed in the sixth or seventh decade of life. Carcinoma is rarely associated, and death from systemic complications such as amyloidosis,[31] malnutrition, and genitourinary disorders, is unusual if the patient is adequately followed.

Treating the patient medically with the aim of maintaining him in the best nutritional condition and as comfortable as possible may avoid further extension of the disease by surgery. The diet should be bland to relieve pain and diarrhea. Foods that are known by the patient to stimulate peristalsis should be avoided. Supplementary feedings high in calories and proteins, vitamins, bedrest, and sedatives should be enhanced in the underweight, undernourished patient. Steroid therapy is less effective than in chronic ulcerative colitis,[10] although uncommonly it induces a complete clinical remission. It should be used in adequate dosage in patients with active disease of short duration which has not responded to the medical measures already mentioned. An episode of intestinal obstruction, occurring in recently symptomatic patients, usually responds surprisingly well to corticotropin associated with intestinal tube decompression. In these acute episodes doses of corticotropin in intravenous drip of 20 to 40 units in 1000 ml. of 5 per cent dextrose in water over a period of 8 hours should be used, followed by prednisone in a gradually decreasing dose, orally. Frequently these patients can be maintained for months or years in an acceptable nutritional condition, and with minor symptoms compatible with normal activity, with prednisone at a low dose of 5 to 10 mg. per day. Adrenal steroid treatment is especially indicated in the extensive ileojejunitis in which resection is impractical and in patients with recurrent disease after surgery. Antibiotic therapy should be restricted to the febrile patient suspected or proved to have internal fistula and abdominal abscess. Bargen[1] has employed radiation therapy with variable results.

The indications for surgery are abdominal abscess, internal and external abdominal fistula, intestinal obstruction developing in longstanding disease, massive bleeding, presence of systemic complications such as amyloidosis, and anal or perianal extensive fistula which may destroy the anal sphincter mechanism.

SUMMARY

The distinguishing features between chronic ulcerative colitis and granulomatous colitis have been described. The difficulties and unresolved problems in the treatment of granulomatous colitis have been stressed. The pathology, clinical characteristics, complications, and results of treatment in regional enteritis have been reviewed.

REFERENCES

1. Bargen, J. A.: Non-surgical management of regional enteritis. J.A.M.A., *165*:2045, 1957.
2. Bargen, J. A., Morson, B., and Brown, C. H.: Panel discussion. Gastroenterology, *51*:806, 1966.
3. Bockus, H. L.: Regional enteritis. *In* Gastroenterology. 2nd ed. Philadelphia, W. B. Saunders Co., 1964, Vol. 2, p. 226.
4. Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D.: Regional ileitis. J.A.M.A., *99*:1323, 1932.
5. Faila Alvarez, L., and Albacete, R.: Further experience with regional enteritis in Cuba. South. M. J., *51*:1556, 1958.
6. Goldberg, H. I.: Focal ulcerations of the colon in granulomatous colitis. Amer. J. Roentgen., *101*:296, 1967.
7. Guckian, J. C., and Perry, J. E.: Granulomatous hepatitis: an analysis of 63 cases and review of the literature. Ann. Int. Med., *65*:1081, 1966.
8. Gump, F. E., Lepore, M., and Barker, H. G.: Ann. Surg., *166*:942, 1967.
9. Hawk, W. A., and Turnbull, R. B., Jr.: Primary ulcerative disease of the colon. Gastroenterology, *51*:802, 1966.
10. Howel Jones, J., and Lennard-Jones, J. E.: Corticosteroids and corticotropin in the treatment of Crohn's disease. Gut, 7:181, 1966.
11. Howel Jones, J., Lennard-Jones, J. E., and Lockhart-Mummery, H. E.: Experience in the treatment of Crohn's disease of the large intestine. Gut, 7:448, 1966.
12. Janowitz, H. D., and Present, D. H., Granulomatous colitis – Pathogenetic concepts. Gastroenterology, *51*:778, 1966.
13. Janowitz, H. D., Lindner, A. E., and Marshak, R. H.: Granulomatous colitis. J.A.M.A., *191*:825, 1965.
14. Korelitz, B. I.: Clinical course, late results and pathological nature of inflammatory disease of the colon initially sparing the rectum. Gut, 8:281, 1967.

15. Lennard-Jones, J. E., and Stalder, G. A.: Prognosis after resection for chronic regional ileitis. Gut, *8*:332, 1967.
16. Lindner, A. E., Marshak, R. H., Wolf, B. S., and Janowitz, H. D.: Granulomatous colitis. New Eng. J. Med., *269*:379, 1963.
17. Lockhart-Mummery, H. E., and Morson, B. C.: Crohn's disease of the large intestine. Gut, *5*:493, 1964.
18. Menin, W., and Behrend, A.: Regional enteritis with free perforations. Ann. Surg., *149*:140, 1959.
19. Neely, J. C.: Perforation in regional enteritis. J.A.M.A., *174*:1680, 1960.
20. Neuman, H. W., and Dockerty, M. B.: The pathology of regional (segmental) colitis. Surg. Gynec. Obstet., *99*:572, 1954.
21. Neuman, H. W., Bargen, J. A., and Judd, E. S., Jr.: A clinical study of 201 cases of regional (segmental) colitis. Surg. Gynec. Obstet. *99*:563, 1954.
22. Rappaport, H., Burgoyne, F. H., and Smetana, H. F.: Pathology of regional enteritis. Mil. Surgeon, *109*:463, 1951.
23. Reeves, B. F., Carlson, H. C., and Dockerty, M. B.: Segmental ulcerative colitis versus segmental Crohn's disease of the colon. Amer. J. Roentgen., *99*:24, 1967.
24. Siegel, R., and White, B. V.: Acute regional ileitis. Conn. Med. J., *17*:738, 1953.
25. Sparberg, M., Fennessy, J., and Kirsner, J. B.: Ulcerative prostitis and mild ulcerative colitis: A study of 220 patients. Medicine, *45*:391, 1966.
26. Stauffer, M. H., Sauer, W. G., Dearing, W. H., and Baggenstoss, H. H.: The spectrum of cholestatic hepatic disease. J.A.M.A., *191*:829, 1965.
27. Stauffer, M. H., Sauer, W. G., Dearing, W. H., and Baggenstoss, H. H.: Biliary tract carcinoma: A complication of liver disease with ulcerative colitis. Gastroenterology, *50*:401, 1966.
28. Van Patter, W. N., Bargen, J. A., Dockerty, M. B., Feldman, W. H., Mayo, C. W., and Waugh, J. M.: Regional enteritis. Gastroenterology, *26*:347, 1954.
29. Warren, K. W., Athanassiades, S., and Monge, J. I.: Primary sclerosing cholangitis. Amer. J. Surg., *111*:23, 1966.
30. Wells, C.: Ulcerative colitis and Crohn's disease. Ann. Roy. Coll. Surg., *11*:105, 1952.
31. Werther, J. L., Shapira, A., Rubinstein, O., and Janowitz, H. D.: Amyloidosis in regional enteritis: A report of 5 cases. Amer. J. Med., *29*:416, 1960.
32. Wolf, B. S., and Marshak, R. H.: Granulomatous colitis (Crohn's disease of the colon); roentgen features. Amer. J. Roentgen., *88*:662, 1962.

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422

Gastrointestinal Disease and Clinical Nutrition

JAMES A. HALSTED, M.D.*

The purpose of this article is to focus attention on the relationship of gastrointestinal disease to nutrition. Clinical nutrition as an entity is a neglected area in medical thinking, medical education, and research, even though many aspects of medicine and clinical research do, in fact, involve nutrition. Malnutrition may arise from an inadequate or insufficient diet, in which case it can be termed *primary*. It may also arise from disordered gastrointestinal function. In this instance the term "conditioned malnutrition" seems an appropriate one. Conversely, a faulty diet may lead to lesions of the gastrointestinal tract or to disordered function. Although it will not be possible to document all instances either of faulty intake of nutrients leading to gastrointestinal disorder, or of malnutrition stemming from gastrointestinal disease, outstanding examples of each will be cited in order to call attention to the importance of clinical nutrition in gastroenterology.

Both gastroenterology and clinical nutrition are broad headings, neither being easy to define with entire satisfaction. Therefore it seems worthwhile to attempt definitions which are at least plausible and to discuss some of the close relationships of nutrition and gastrointestinal disease.

It may be obvious that essentially all aspects of biology and medicine are intimately related to nutrition at one level or another. However, a certain area can be delineated, called clinical nutrition. Such delineation as it is proposed to make will not be agreed upon by everyone concerned with nutrition and it is undoubtedly arbitrary. Nevertheless it may be useful as a means of defining a clinical area if not a true scientific discipline. Thus clinical nutrition may be defined as the area of human disease states or malnutrition brought about by (1) faulty intake of nutrients, or factors which cause their unavailability for absorption; (2) faulty digestion, absorption, or excretion of nutrients; or (3) faulty metabolism of nutrients.

---

*Associate Chief of Staff for Research and Education, Veterans Administration Hospital; Professor of International Health, Department of Epidemiology and Environmental Health, George Washington University School of Medicine, Washington, D.C.

The first criterion in this definition of clinical nutrition is more the concern of the dietitian, the agriculturalist, the Public Health officer, the health educator, and the psychologist than it is of the gastroenterologist. Nevertheless, primary dietary defects may cause gastrointestinal disorders, examples of which will be cited. The third criterion, faulty metabolism of nutrients, is generally beyond the realm wherein gastrointestinal disease is involved in nutrition. It falls chiefly in the province of the biochemist, the specialist in metabolism or diabetes, the endocrinologist, and often the hematologist.

In discussing the relationship of gastroenterology to clinical nutrition we must be concerned chiefly with the second of the three identified criteria, namely abnormalities of digestion, absorption, or excretion of nutrients. However, the relationships between nutrition, metabolic and hormonal processes, and gastroenterology are close. The more that is understood the more blurred become the lines demarcating disciplines and the more important it is for collaboration to take place between workers in different areas of scientific research, especially between gastroenterologists and those interested in clinical nutrition.

It is unnecessary to belabor a definition of gastroenterology. It consists of the physiology, pathology, and clinical aspects of the tubular gastrointestinal tract and of the solid organs – the pancreas and liver. Abnormalities which lead to faulty digestion, absorption, or excretion usually lead to malnutrition. This is why it is reasonable to define malnutrition secondary to gastrointestinal disease as "conditioned malnutrition." Thus it becomes a major component of the area of medicine called clinical nutrition.

Liver disease is, of course, closely involved with malnutrition. Through its involvement with metabolic processes it may be the cause of malnutrition, and, conversely, malnutrition may be one causative factor in cirrhosis. However, liver disease will not be considered in this article since it is well covered elsewhere in this volume.

Disorders of the pancreas often lead to conditioned malnutrition through interference with aspects of the digestive process. These also are considered elsewhere so will not be dealt with further.

GASTROINTESTINAL DISORDERS CAUSED BY FAULTY DIET

Zubiràn[19] has called attention to a number of gastrointestinal abnormalities stemming from primary malnutrition in Mexico. Most of these examples are seen in poverty areas in underdeveloped countries where crowding, a high incidence of infectious diseases, impoverished education, and illiteracy are the rule. The syndrome of protein-calorie malnutrition – kwashiorkor or protein deficiency – leads to a fatty liver, pancreatic dysfunction, and often intestinal malabsorption. Diarrhea is common. A thorough study by Zubiràn of 92 patients with primary malnutrition revealed tongue abnormalities, diarrhea, abdominal pain, nausea, vomiting, and distention in from 29 to 86 per cent. Blood and mucus were found in 41 per cent of the patients with diarrhea, although parasites and intestinal pathogens were not present. In 28 per cent steatorrhea and creatorrhea occurred. Intestinal biopsies showed findings ranging from normal to partial villous atrophy. *d*-Xylose tests were frequently abnormal. Radiologic study often revealed dilated loops with segmentation of barium and the "moulage sign."

Not all instances of faulty diet leading to gastrointestinal disease occur in the underdeveloped areas of the world. Thus Naiman et al.[14] studied the effects of a milk diet on 14 infants in Boston. This produced severe iron-deficiency anemia and was associated with achlorhydria in 4 of 8 patients, impaired *d*-xylose absorption in 6 of the 14, low serum carotene in 5 of the 14, and a flat vitamin A tolerance curve in 10. Stool fat excretion was increased in 4 of the group, and positive tests for occult blood occurred in 4 patients. Intestinal biopsy showed abnormalities in 7 of the 11 patients in which it was performed. Most of these abnormalities of intestinal integrity and function reverted to normal after adequate treatment with iron. It was concluded that nutritional iron deficiency in infants on an exclusively milk diet may lead to a diffuse enteropathy with malabsorption and achlorhydria.

Although severe iron deficiency of nutritional origin was seen in 11 patients with dwarfism and hypogonadism studied in Iran, this group did not have abnormalities of intestinal absorption. There were normal *d*-xylose tests, absence of excess fat in the stools, normal absorption tests for iron, negative tests for occult blood, and normal gastrointestinal x-ray studies. Intestinal biopsies performed in six of the group showed normal structure. However histamine-fast achlorhydria occurred in six out of eight of the patients in whom the test was performed. In only two of the six could the test be repeated after 6 weeks and 6 months respectively, when the anemia was cured by iron therapy. In these two gastric secretion had not reverted to normal.[7] Achlorhydria has long been noted in patients with iron-deficiency anemia.[4, 12] Whether achlorhydria is the result rather than an etiologic factor in iron-deficiency anemia is debatable, although most workers believe it is a result.[1]

Chronic iron lack has been known since 1893[2] to be related to dysphagia. This can be cured by iron therapy and dilatation of the esophagus, which may contain webs or strictures. Known in this country as the Plummer-Vinson syndrome,[17] it has been termed sideropenic dysphagia in Sweden – probably a better term.[18]

Vitamin deficiencies from faulty intake are well known to produce gastrointestinal disorders. Thus niacin deficiency is associated with diarrhea in pellagra. Cheilosis and changes in the tongue occur with deficiencies of riboflavin and other B vitamins. Folic acid and vitamin B_{12} deficiencies are related to tropical sprue, since treatment with these vitamins is usually quite beneficial (see p. 1367).

Although intestinal parasites are a major cause of illness, their relationship to gastrointestinal disease might be considered to be one of harmless guest or resident in many instances. However there are, of course, many parasites of which this is not the case. Giardia lamblia may cause malabsorption and steatorrhea. Ancylostoma duodenale and Necator americanus both cause chronic gastrointestinal bleeding with anemia. If this is prolonged from childhood years, dwarfism, hepatosplenomegaly, and hypogonadism may result. The first example of this was reported in 1910.[13] (The endocrine abnormalities might actually be caused by zinc deficiency because red blood cells contain considerable zinc. Animals with experimental zinc deficiency have growth failure and hypogonadism.) Finally Chagas' disease (Trypanosoma cruzi, South American trypanosomiasis) may cause megacolon or megaesophagus from damage to Auerbach's plexus.

CONDITIONED MALNUTRITION IN GASTROINTESTINAL DISEASE

Most of the significant instances of malnutrition secondary to, or conditioned by, gastrointestinal abnormalities have been considered in the articles in this volume on Malabsorption, Disaccharidase Deficiency, and Tropical Sprue. The article on Inflammatory Disease of the Bowel makes mention of the nutritional effects of regional enteritis, where steatorrhea and malabsorption of vitamin B_{12} may occur. Likewise in granulomatous colitis, which involves the ileum, vitamin B_{12} deficiency may result, since this is the site of absorption of that vitamin. Ulcerative colitis is usually associated with malnutrition, although not because malabsorption occurs, the colon being an organ of excretion. Fever, toxicity, anorexia, and loss of blood and nitrogen from colonic exudate may all combine to lead to severe malnutrition in chronic ulcerative colitis.

Diseases of the stomach which lead to specific types of malnutrition should be considered. In 1957 Citrin, Sterling, and Halsted[3] described protein loss from the stomach in a patient with Menetrier's disease who had severe hypoproteinemia. Studies with radioactive iodinated serum albumin (RISA) demonstrated that a large amount of radioactivity was excreted into the stomach and that there was a much reduced protein pool. This led to further studies by Gordon[6] and by many others resulting in the concept of protein-losing enteropathy.[11]

The nutritional effects of subtotal and of total gastrectomy have been analyzed.[8, 10] Significantly, it has been demonstrated that gastrectomy results in steatorrhea and weight loss in a large proportion of patients. After total gastrectomy these occur in practically all cases. The mechanism of steatorrhea is not clear. However, poor mixing with bile and pancreatic juice from loss of the reservoir function of the stomach, and perhaps (in the case of subtotal gastrectomy) deleterious effects of an abnormal bacterial flora residing in the blind loop of duodenum which is produced in the Billroth II anastamosis,[5] are important factors. The cause of the weight loss is chiefly a reduction in caloric intake due to the small or absent stomach remnant, with early satiety and discomfort when normal-sized meals are taken.

Iron deficiency of mild degree is the rule after both subtotal and total gastrectomy. The mechanism of this is not clear. Depletion of iron stores by chronic blood loss from the lesion for which the operation was performed may be a significant factor. Achlorhydria resulting from the operation may be another; reduction of food iron to the absorbable divalent ferrous form takes place optimally in an acid medium. Finally, rapid passage through the upper bowel must be an important additonal factor, because iron is normally absorbed in the duodenum.

Treatment of steatorrhea which follows gastrectomy is difficult and unsatisfactory. Frequent small feedings, up to 8 or 10 per day, may help. Use of antibiotics to change the abnormal bacterial flora in the duodenal loop has been shown to lessen steatorrhea.[5] Treatment of iron deficiency may be most effective when a liquid iron preparation is given in a large dose at bedtime while the patient is recumbent. This may allow more time for the iron to be in contact with absorbing surfaces and to obviate the necessity of digesting coated iron tablets.

It was long believed that intrinsic factor was secreted in the duodenum as well as the stomach because hog intestine had been shown to have intrinsic factor properties of facilitating absorption of vitamin B_{12}. However, absorption of radioactive vitamin B_{12} was shown not to occur at all after total gastrectomy; this demonstrated that intrinsic factor was limited to the stomach in man.[9, 16] Further studies by Swendseid et al.[15] demonstrated that the liver contained on the average about 1 mg. of vitamin B_{12}. Because the daily requirement of this vitamin is between 0.5 and 1.0 μg., this would provide a storehouse sufficient to last 3 to 6 years after absorption ceases, as it does following total gastectomy. It is generally agreed that all patients surviving a total gastrectomy long enough for the liver stores to be used up will develop megaloblastic anemia, indistinguishable from Addison's pernicious anemia, unless prophylactic (replacement) therapy is instituted. Both clinical observations and theoretical considerations substantiate this fact.

Theoretically, vitamin B_{12} ought to be absorbed normally after subtotal gastrectomy because the proximal end of the stomach is a rich source of intrinsic factor secretion. However, assays of vitamin B_{12} in the serum of patients who have had subtotal gastrectomy often show a deceasing concentration as time goes on, indicating that deficiency with megaloblastic anemia may ultimately occur unless replacement therapy is instituted. Clinically, however, this is quite rare.

As a result of these studies of the relationship of gastrectomy to vitamin B_{12} deficiency, all patients who have had a total gastrectomy should receive an intramuscular injection of 50 μg. of vitamin B_{12} once a month to prevent the development of megaloblastic anemia. This is not recommended for the patient with a subtotal gastrectomy unless periodic blood study reveals an increasing anemia. Then a bone marrow examination is indicated. Assay of serum for vitamin B_{12}, if the test is available, should be done, as well as a Schilling test for vitamin B_{12} absorption. If these examinations indicate vitamin B_{12} deficiency, treatment should be instituted.

SUMMARY

The relationships of gastrointestinal disease and nutrition are discussed. An attempt has been made to define and delineate the field of clinical nutrition.

Examples of the effect of primary or dietary malnutrition on gastrointestinal structure and function are given.

The mechanisms of examples of conditioned malnutrition secondary to gastrointestinal dysfunction in certain pathologic states are discussed. Treatment is discussed briefly where pertinent.

REFERENCES

1. Badenoch, J., Evans, J. R., and Richards, W. C. D.: The stomach in hypochromic anaemia. Brit. J. Haemat., *3*:175-185, 1957.
2. Blankenstein, P.: Dysphagia hysterica. Dissertation, University of Bonn, 1893.
3. Citrin, Y., Sterling, K., and Halsted, J. A.: The mechanism of hypoproteinemia associated with giant hypertrophy of the gastric mucosa. New Eng. J. Med., 257:906-912, 1957.
4. Davidson, W. M. B., and Markson, J. L.: Gastric mucosa in iron deficiency anemia. Lancet, 2:639, 1955.
5. Goldstein, F., Wirts, C. W., and Kramer, S.: The relationship of afferent limb stasis and bacterial flora to the production of postgastrectomy steatorrhea. Gastroenterology, *40*:47-55, 1961.
6. Gordon, R. S., Jr.: Exudative enteropathy. Abnormal permeability of the gastrointestinal tract demonstrable with labeled polyvinylpyrrolidone. Lancet, *1*:325, 1959.
7. Halsted, J. A., Prasad, A. S., and Nadimi, M.: Gastrointestinal function in iron-deficiency anemia. Arch. Int. Med. *116*:253-256, 1965.
8. Halsted, J. A., Briggs, J. D., and Gasster, M.: Nutritional problems after total gastrectomy. New York State J. Med., 57:223-230, 1957.
9. Halsted, J. A., Gasster, M., and Drenick, E. J.: Absorption of radioactive vitamin B_{12} after total gastrectomy: Relation to macrocytic anemia and to the site of origin of Castle's intrinsic factor. New Eng. J. Med., *251*:161-168, 1954.
10. Hastings, N., Halsted, J. A., Woodward, E. R., Gasster, M., and Hiscock, E. A.: Subtotal gastric resection for peptic ulcer. A.M.A. Arch. Surg., *76*:74-80, 1958.
11. Jarnum, S.: Protein-Losing Gastroenteropathy. Philadelphia, F. A. Davis Co., 1963.
12. Lees, F., and Rosenthal, F. D.: Gastric mucosal lesions before and after treatment in iron deficiency anemia. Quart. J. Med., 27:19, 1958.
13. Lemann, I. I.: A study of the type of infantilism in hookworm disease. Arch. Int. Med., 6:139-146, 1910.
14. Naiman, J. L., Oski, F. A., Diamond, L. K., Vawter, G. F., and Schwachman, H.: The gastrointestinal effects of iron-deficiency anemia. Pediatrics, *33*:83-99, 1964.
15. Swendseid, M. E., Hvolball, E., Schick, G., and Halsted, J. A.: The vitamin B_{12} content of human liver and its nutritional significance. Blood, *12*:24-28, 1957.
16. Swendseid, M. E., Halsted, J. A., Libby R. L.: Excretion of Co^{60}-labeled vitamin B_{12} after total gastrectomy. Proc. Soc. Exp. Biol. Med., *83*:226-228, 1953.
17. Vinson, P. P.: Hysterical dysphagia. Minn. Med., *5*:107-108, 1922.
18. Waldenstrom, J., and Kjellberg, S. R.: Roentgenological diagnosis of sideropenic dysphagia (Plummer-Vinson's syndrome). Acta radiol., *20*:618-638, 1939.
19. Zubiràn, S.: Nutritional aspects of gastrointestinal disease. Amer. J. Digest. Dis., 6:336-350, 1961.

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422

Some Implications of Current Research in Hepatology

HYMAN J. ZIMMERMAN, M.D.*

Hepatology has benefitted from the biological revolution and has suffered from the literature explosion. Accordingly, it is possible to see a number of areas where important advances have occurred, but it is also bewilderingly difficult to select the areas that most warrant listing among the recent advances in the understanding of liver diseases. Studies with the electron microscope have provided considerable information on the ultrastructural changes in a variety of clinical hepatic injuries, and have permitted increased insight into their pathogenesis. The electron microscope, however, has found no place in clinical hepatology as yet.

The advances in hepatic physiology have uncovered a group of inborn and acquired errors of bilirubin metabolism, which are discussed elsewhere (see p. 1417). Studies on the mechanism by which sulfobromophthalein is cleared by the liver by the use of mathematical and experimental models, have demonstrated that the dye is removed from the bloodstream, stored, conjugated, and excreted, each as discrete steps. These studies have enhanced the usefulness of dye excretions as a diagnostic measure and an experimental tool. The methods available for the study of hepatic disease have been outlined in the paper by Schimmel (p. 1407).

Perhaps one of the most exciting developments in hepatic physiology has been the demonstration of the role of the liver in the metabolism of drugs and other foreign chemicals. The biochemical mechanisms by which these substances are modified by the liver have been clarified by a number of elegant studies. A large number of studies also have demonstrated that the ability of the liver to metabolize compounds can be enhanced to a remarkable degree by exposure to other agents (e.g., phenobarbital). The enhancement has been shown to be accompanied by an increase in the amount of endoplasmic reticulum and in its content of drug-metabolizing enzymes.

A great deal of attention has been devoted to the study of hepatotoxi-

---

*Chief, Medical Service, Veterans Administration Hospital; Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts

city. A huge number of botanical and synthetic agents that are able to produce hepatic injury have been identified. These can be categorized according to presumed or demonstrated mechanisms of injury and according to the form of the hepatic injury produced. While the unpredictability of some forms of drug-induced hepatic disease continues to plague hepatotoxicologists, the approach to this facet also has been refined. Some drugs, such as the C-17 alkylated anabolic agents (methyltestosterone, norethandrolone), appear to interfere with hepatic function because of intrinsic properties of the molecule, rather than the more capricious circumstances of host idiosyncracy. Apparently related to this problem is the hepatic dysfunction and jaundice produced by oral contraceptive agents and the interesting recent observation that females prone to develop jaundice of pregnancy are more susceptible to this adverse effect of the steroid. This has permitted speculations regarding the mechanism of both the jaundice of pregnancy and that by which certain steroidal agents interfere with hepatic function.

An important development in hepatotoxicity is the demonstration that a curious form of fatty metamorphosis can be produced by large intravenous doses of tetracycline and that this lesion resembles the acute fatty liver of pregnancy. Indeed, the accumulated data have made it possible to recognize that some hepatotoxins, or their metabolic products, cause hepatic injury by disruption of intracellular membranes, others by specific interference with hepatic cell metabolism, and others by specific interference with the bilirubin transport mechanism. Other agents, however, produce hepatic injury by dependence on host idiosyncracy in the form of drug allergy or unique metabolic aberrations. In that category appears to be the jaundice that has followed exposure to halothane. While of extremely low incidence in exposed persons, it has produced a characteristic lesion in some recipients.

Of great importance in the studies of hepatotoxicity is the recent development of knowledge regarding the botanical hepatotoxins. While some have been recognized for a long time (Amanita phalloides and the pyrrolizidine alkaloids), others have appeared on the scene more recently. Several mycotoxins may prove to be of great importance. Enormously potent substances produced by Aspergillus flavus (aflatoxin) and Penicillium islandicum (luteoskyrin) have been shown to produce necrosis, cirrhosis, or hepatoma in experimental animals. Significant circumstantial evidence has been derived from epidemiologic studies to support the view that some forms of chronic hepatic disease and carcinoma of the liver in some parts of the world might be the result of contaminations of food by fungal hepatotoxins. While circumstantial, the evidence is impressive and awaits confirmation.

Related to the studies of hepatotoxicity is the mounting and conclusive evidence that alcohol can produce hepatic injury quite independent of the effects of alcoholism or nutrition. Studies in several laboratories have demonstrated that alcohol can lead to deposition of fat in the liver by increased synthesis of the lipid, by interfering with the mechanisms for removal of lipid from the liver, by increased mobilization of lipid to the liver, by interference with oxidation of lipids by the liver, and perhaps additionally, by increasing the requirements for choline. Whether the ability of alcohol to induce fatty metamorphosis explains the pathogenesis of the cirrhosis of alcoholism, however, remains to be demonstrated. The view continues to the present that fat deposition in the liver alone does not lead to cirrhosis, but that, in addition to fatty change, there must be other hepatic injury (necrosis) to produce cirrhosis. The mechanism by which the curious histologic feature "alcoholic hyaline" (Mallory body) is produced also remains to be understood. Whether it is the product of alcohol, malnutrition, or some adventitious toxic agent, remains to be understood. The evidence for an adverse effect of alcohol does not preclude the relevance of the malnutrition of the alcoholic as an etiologic factor in cirrhosis. These and other aspects of cirrhosis are considered in the thorough analysis of the disease by Leevy (p. 1445).

An interesting development of the past decade is the observation of the high incidence of morphologically categorizable postnecrotic cirrhosis in alcoholic patients. Presumably, this represents the morphologic eventuation in the course of Laennec's cirrhosis. It may also represent, however, overlooked etiologic factors.

The significance of postnecrotic cirrhosis remains an enigma. The form which might be called "active" postnecrotic cirrhosis has also gone under the name of "chronic active hepatitis" and "juvenile cirrhosis." It is characterized by marked hyperglobulinemia, and by various serologic and other features that suggest "autoimmune" pathogenesis. These features include the frequent presence of striking aggregates of plasma cells in the liver, and of antinuclear and other antibodies in the serum. Nicknames such as "lupoid hepatitis" or "lupoid cirrhosis," which have been applied, transmit the view that the entity is a manifestation of systemic lupus erythematosus expressed as liver disease. A more acceptable view considers the entity to be a form of autoimmune liver disease with serologic features that overlap those of S.L.E., but that the two are independent conditions. Recent studies that have demonstrated serologic differences between "lupoid" chronic liver disease and systemic lupus erythematosus may provide tools for insight into the problem.

Impressive serologic evidence has been provided to support the view that primary biliary cirrhosis is an autoimmune disease. Studies in several laboratories have shown that the serum of patients with this form of liver disease contains an antibody-like substance that can react with a mitochondrial antigen. Consistent with this view is the observation that some forms of drug-induced hepatic injuries (chlorpromazine jaundice), which appear to be the result of a hypersensitivity disease, may eventuate in a chronic, but apparently reversible, illness closely resembling primary biliary cirrhosis.

Several syndromes of chronic intrahepatic cholestasis have been unraveled during the past decade. One is the form of intraheptic cholestasis associated with ulcerative colitis. It appears to be quite distinctive and may be an extreme manifestation of the more commonly observed "pericholangitis" seen in ulcerative colitis. A syndrome that resembles primary biliary cirrhosis may also be observed in association with sarcoidosis. Of interest in this regard is the observation that some patients with primary biliary cirrhosis show an impressive granulomatous lesion in the liver. Indeed, the distinction of primary biliary cirrhosis with a granulomatous response from sarcoidosis with intrahepatic cholestasis remains to be defined clearly. The past decade has seen reports of a number of instances of sclerosing cholangitis, both primary and secondary.

Somewhat disappointing has been the slow progress in the understanding of hepatitis, hepatic coma, and portal hypertension. The problems of hepatic coma and portal hypertension are reviewed by Chalmers and Conn, respectively. An extensive literature continues to accumulate on viral hepatitis, but there has been distressingly little definitive progress in its specific diagnosis, prevention, and treatment. The virus which from indirect criteria is recognized to be the cause of hepatitis remains elusive. The many efforts to isolate the agent in tissue culture have yielded a number of leads. Some isolates have been clearly set aside as irrevelant, others remain to be substantiated. Indeed no reliable means for culturing the agent(s) of viral hepatitis is yet available. Until a method becomes available, efforts to confirm etiologic diagnosis, develop a vaccine or to study potential therapeutic agents, remain beyond reach.

A brighter aspect is the recent support for the prediction of many years ago, that the most fruitful animal for study of hepatitis would probably be the primate. Recent convincing epidemiologic studies support the view that chimpanzees may be carriers of the virus of human hepatitis. Relevant to this observation, is the evidence that the marmoset may be a suitable experimental model for the study of hepatitis. However, the usefulness of these observations remains to be established. No chemotherapeutic agent has been developed that is of any promise in the treatment of viral hepatitis. The usefulness of gamma globulin in the prevention of clinical hepatitis has been demonstrated and extended during the past decade. There is little doubt that the clinical expression of infectious hepatitis (IH or viral hepatitis) can be prevented by gamma globulin administered at the appropriate interval after exposure. It seems clear, however, that the disease is muted, not prevented. While this is useful in dealing with epidemics and with persons who are considered a poor risk for the disease, such as patients in the last trimester of pregnancy, the ultimate impact on the life history of hepatitis in the individual patient remains to be clearly defined. More frustrating is the appraisal of the value of gamma globulin in the prevention of post-transfusion hepatitis. After two decades of wondering and of conflicting reports, it can only be hoped that the question will be answered by cooperative studies now being conducted on a national scale.

Lack of space precludes reference to other facets of hepatology that have been studied recently. The foregoing comments have drawn attention to the problems that appeared to this reviewer to be of greatest interest and importance.

Veterans Administration Hospital
150 South Huntington Avenue
Boston, Massachusetts 02130

Diagnostic Procedures in Liver Disease

ELIHU M. SCHIMMEL, M.D.*

The diagnosis and management of liver disease depends on a broad clinical analysis of many factors in the patient's history, physical findings, and laboratory data. It is a truism that a careful and complete record of the medical history provides the primary diagnostic information. Furthermore, the physical examination will often provide necessary evidence for the diagnosis of liver disease. The experienced clinician rapidly masters the skills needed to acquire these data which, in most instances, are the most important diagnostic procedures. Dr. Alvan Feinstein[6] has discussed in detail the special type of reasoning, called "clinical judgment," which physicians use in interpreting these data.

CLINICAL DIAGNOSIS

A prospective study[10] of clinical judgment in liver disease is illustrated in Table 1. The diagnostic accuracy of several physicians was compared before and after laboratory findings were added to the primary clinical data of the patients' history and physical examination.

To confirm his clinical impression and to assist him in more difficult cases, the physician turns to the many ancillary diagnostic procedures which are performed in the clinical laboratory or are available only through the specialized facilities and techniques of other medical disciplines. Sophistication in the art of medical practice is needed to select the most valuable among these many procedures and to interpret their relevance to the problem at hand. The physician will order various tests to answer the following questions:

1. Is liver disease present?
2. Can the etiology be determined?
3. What is the extent of liver dysfunction?

In most clinical situations, however, the physician must not be misled by relying too greatly on a laboratory study. Few of these tests can be considered specific for liver function; systemic disease, cardiovascular failure, nutritional deficiency, infections, and bone disease are a few of the many disorders which affect the results of liver function tests.

---

*Chief, Gastroenterology Section, Veterans Administration Hospital; Assistant Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts

Table 1. *Diagnostic Accuracy in Liver Disease**

INFORMATION AVAILABLE	% CORRECT DIAGNOSES CIRRHOSIS	EXTRAHEPATIC OBSTRUCTION	VIRAL HEPATITIS
History and physical	80.0%	77.4%	70.1%
Clinical and laboratory	86.5%	90.3%	70.1%

*Adapted from Schenker, S., et al.: Amer. J. Digest. Dis., 7:449, 1962.

Furthermore, the liver's functions are complex and interrelated, dependent on blood supply, parenchymal metabolism, and the reticuloendothelial Kupffer cells. Because of the liver's functional reserve, none of the various studies with "normal" results can exclude liver disease. Clinicians, therefore, have developed the concept of a "battery" or "profile" of liver function tests designed to get the most useful diagnostic information. Lastly, when laboratory studies are used for management – following the course of the disease, assessing the response to therapy, and attempting a prognosis – these studies must be repeated at frequent intervals during the patient's illness.

This discussion of diagnostic procedures will follow the clinical pattern in which the patient's work-up usually proceeds – from routine clinical studies to more complex and specialized investigations, from the simple collection of blood samples to the more rigorous approaches which often entail a significant morbidity and measurable risk of fatal complications. Concepts of the pathophysiology of liver disease would suggest a quite different organization in terms of circulatory, metabolic, reticuloendothelial, and excretory functions of the liver. Liver disease in clinical situations, however, nearly always involves these functions simultaneously and makes such a division artificial in light of the needs of patient care. Considerations of methodology are omitted here, and a text on clinical pathology should be consulted for specific laboratory techniques.[1] In spite of the enormous number of procedures available, this article will present a working outline of those few procedures which best answer the questions outlined above and which are within the capability of most hospitals. Such a guide to diagnostic procedures in liver disease is outlined in Table 2.

ROUTINE HEMATOLOGIC SURVEY. The anemia of chronic liver disease depends on many intermediary factors, among which are (1) hypersplenism, (2) chronic blood loss and iron deficiency, (3) hemolysis, (4) nutritional deficiency, particularly of folic acid, and (5) a poorly understood bone marrow depression in the presence of active liver disease. Polycythemia may be a disgnostic clue for hepatoma. Changes in the white blood count are not specific except insofar as they suggest hypersplenism (leukopenia) or a superimposed inflammatory or infectious process (leukocytosis). Lymphocytosis is often noted in viral infections of the liver.

ROUTINE X-RAY STUDIES. Liver size is poorly estimated from films of the chest and abdomen, although abscess or malignant masses within

Table 2. *A Guide to Diagnostic Procedures*

- History
- Physical examination
- Routine hematologic survey
- Routine x-ray studies
  - Chest film
  - Plain film of the abdomen
  - Barium studies of the gastrointestinal system
- Biochemical studies of the blood
  - Serum bilirubin, total and direct
  - Serum alkaline phosphatase
  - Other enzymes
    - Serum glutamic oxalacetic transaminase (SGOT)
    - Serum glutamic pyruvic transaminase (SGPT)
    - Lactic dehydrogenase
  - Serum proteins, total and albumin fraction
    - Electrophoresis
  - Thymol turbidity and flocculation tests
  - Bromsulphalein (BSP) excretion
  - Blood ammonia
- Bile pigment excretion
  - Urine
    - Bilirubin
    - Urobilinogen
  - Stool color and fecal stercobilinogen
- Coagulation studies
  - Prothrombin time, one-stage Quick method
  - Assay of clotting factors V, VII, IX, and X
  - Platelet count
- Radioisotope scans of the liver (hepatic scintillography)
  - Colloidal gold-^{198}Au
  - Rose bengal-^{131}I
- Radiology of the biliary tree
  - Oral cholecystogram
  - Intravenous cholangiogram
  - Percutaneous transhepatic cholangiography
- Assessment of portal hypertension
  - Barium swallow for esophageal and gastric varices
  - Esophagoscopy
  - Splenoportography
  - Splenic pulp pressure
  - Hepatic vein catheterization and wedged pressure
- Needle biopsy of the liver
- Laparotomy
- Other studies
  - Paracentesis
  - Peritoneoscopy
  - Neurologic evaluation and electroencephalogram
  - Selective angiography
  - Serologic studies

the liver may be suggested by changes in the hepatic outline. Gastrointestinal barium studies may show displacement of organs by the liver or other features of importance in the general clinical evaluation, such as varices or the primary site of malignant disease which has metastasized to the liver.

BILIRUBIN. Normal values: Total, 0.2 to 1.2 mg. per 100 ml.; direct, less than 0.3 mg. per 100 ml.

Clinical jaundice is usually detected when the serum bilirubin reaches 2.0 to 3.0 mg. per 100 ml. Serial changes in the total bilirubin concentration are useful in diagnosis and prognosis. A sharp rise or fall in bilirubin suggests passage of a gallstone; persistently high elevations most commonly mean extrahepatic obstruction. Isolated values, however, are not to be trusted in differential diagnosis or in the estimation of severity of disease.

In hemolytic jaundice, direct (conjugated) bilirubin remains low, usually 5 to 15 per cent of the total. Otherwise, the ratio of direct total bilirubin is not considered of diagnostic importance in the differential diagnosis of liver disease.

ALKALINE PHOSPHATASE. Normal value: 1.5 to 4.5 Bodansky Units (B.U.)

The sources and fate of serum alkaline phosphatase are not completely understood and the clinical value of this enzyme determination is largely empirical. The presence of bone disease, such as osteomalacia, or hyperparathyroidism, must be excluded before interpreting abnormal results. Parenchymal liver disease usually gives rise to slight elevations (5 to 15 B.U.), whereas extrahepatic obstruction and infiltrative liver disease more often cause large abnormalities (greater than 15 B.U.) Unfortunately, the enzyme is not of value in differentiating intrahepatic cholestasis from extrahepatic obstruction. Other enzymes which reflect obstruction to bile flow (both intrahepatic and extrahepatic) include the serum leucine aminopeptidase, beta-glucuronidase and 5-nucleotidase. These enzymes vary somewhat in their sensitivity and specificity, but occasionally may be useful, since they are unaffected by bone disease.

TRANSAMINASE. Normal values: 5 to 40 Karmen Units.

The serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) have proved to be most useful enzymes in the clinical evaluation of liver disease. These enzymes are most sensitive in the detection of diffuse hepatocellular injury, such as viral hepatitis and toxic or anoxemic liver disease. They are especially useful in the following areas: (1) the detection of subclinical liver disease such as the preicteric phase of hepatitis; (2) the diagnosis of anicteric hepatitis among contacts in an epidemic situation or after blood transfusion; and (3) evaluating the course of subacute and chronic hepatitis. Although peak elevations of these enzymes do not have prognostic value, the persistence of abnormalities is accepted as reliable indication of a continuing inflammatory process. Blood levels of either transaminase greater than 500 units are most uncommon in conditions other than hepatitis or liver anoxia; modest elevations of transaminase have not had value in the differential diagnosis of liver disease. SGPT is more abnormal than SGOT in hepatitis.[3]

LACTIC DEHYDROGENASE. Normal values: 150 to 450 units (values are quite variable with different methods).

Lactic dehydrogenase (LDH) is a useful addition to the battery of enzyme studies, since it is only slightly elevated in most types of liver disease. LDH is much more sensitive to diseases of the myocardium and a variety of anemias, especially hemolytic. It thus has value as an aid in the differential diagnosis of moderate abnormalities of the serum transaminase. In the presence of liver disease, moderate elevations of the LDH suggest malignant disease.

Isoenzymes of LDH may differentiate tissue sources, but are not yet applicable to routine clinical evaluation.

OTHER ENZYMES. A great variety of other enzyme assays have been described which accurately reflect liver disease. These include isocitric dehydrogenase (ICD) and ornithine carbamyl transferase (OCT). Both of these enzymes are more specific for liver cell damage and less influenced by myocardial infarction or other systemic disorders. However, for ordinary clinical use, little is added by these assays.

The pattern of abnormalities seen in a standard group of enzymes has been more useful than the isolation of organ-specific enzyme assays.[12]

SERUM PROTEINS. Normal values: Albumin, 3.5 to 4.5 gm. per 100 ml.; total globulin, less than 3.5 gm. per 100 ml.; gamma globulin, 0.5 to 1.8 gm. per 100 ml.

Neither the total serum proteins nor the A/G ratio are of diagnostic value; information about the serum albumin and serum globulin levels are independently variable and provide different information. Depression of the serum albumin occurs in chronic or massive acute liver disease; albumin may be depressed through renal or intestinal losses as well as through chronic malnutrition. Serum globulin is even less specific an indication of liver disease; it is sensitive to chronic inflammation and fibrotic disorders generally. Electrophoretic patterns with prominent elevation of the gamma globulin over 2.0 gm. per 100 ml. may be a prominent finding in chronic active hepatitis. In general, serum protein changes are nonspecific and insensitive indicators of liver damage.

THYMOL TURBIDITY. Normal values, 0 to 4 units (Shank and Hoagland).

A large number of flocculation and turbidity tests have been described and introduced on empirical grounds for the diagnosis of hepatocellular disorders. These tests primarily reflect increases in the gamma globulin concentration but also depression of the serum albumin. Elevation of blood lipids or lipoproteins also gives positive flocculation and turbidity reactions. These tests are nonspecific and are gradually being abandoned in favor of enzyme assays and serum electrophoresis for the diagnosis of hepatic injury.

The thymol turbidity test has been retained at many institutions because it is easily performed and more quantitative than the flocculation tests. Abnormalities of thymol turbidity are most marked with infectious hepatitis and cirrhosis; acute obstructive biliary disease infrequently gives abnormal results.

BROMSULPHALEIN EXCRETION. Normal values, less than 6 per cent retention at 45 minutes.

A number of dye excretion tests provide the most sensitive indices of hepatic circulation and of parenchymal and excretory functions. Bromsulphalein (BSP) is the most widely accepted of these tests.

BSP is administered in a dose of 5 mg. per kg. body weight as an intravenous injection given slowly over the course of a few minutes. A single blood sample is taken 45 minutes later from the opposite arm. BSP levels over 6 per cent may occasionally be seen in healthy persons who are obese. A number of fatal reactions have been reported, although their estimated incidence is on the order of one per million doses. At many institutions, the use of this test is restricted to those cases in which other liver function studies are normal in the face of suspected liver disease. In the presence of jaundice and other biochemical abnormalities, the BSP is largely superfluous. The BSP test is of little value in the differentiation of hepatic disease from biliary obstruction. Rose bengal and indocyanine green are similar dyes which have no advantage over BSP for ordinary clinical use.

BLOOD AMMONIA. Normal values, 20 to 50 μg. per 100 ml.

The blood ammonia level is an insensitive indication of liver disease and is affected chiefly in terminal or overwhelming liver cell failure, such as end-stage cirrhosis or fulminant hepatitis. In addition, after portacaval shunt for the complications of portal hypertension, the blood ammonia may occasionally be elevated chronically. In all of these situations, there is usually an associated hepatic encephalopathy. This problem is discussed further elsewhere (see p. 1475).

BILE PIGMENT EXCRETION. Normal values: urine bilirubin, absent; urine urobilinogen, 0.5 to 1.5 Ehrlich units per 2-hour sample; stool color, brown; fecal stercobilinogen, 50 to 200 mg. per day.

Important clinical information can be obtained from the serial examination of the urine and stool for bile pigment products. Intrahepatic cholestasis or biliary obstruction result in impaired excretion with light stools and low levels of fecal stercobilinogen; urinary urobilinogen is absent only in high-grade obstruction. Ordinary hepatocellular disease usually causes moderate elevations of the urinary urobilinogen. Significant hemolysis leads to high levels of urinary urobilinogen and fecal stercobilinogen. The increased excretion of fecal bile pigments may be crudely estimated by observing the dark stool color, but quantitative estimation should be performed when the information is of importance.

Urine urobilinogen estimation is subject to diurnal variation; it is best performed by collecting a carefully timed, 2-hour, freshly voided specimen in midafternoon.

Urine bilirubin excretion is an accurate reflection of an elevated level of serum direct (conjugated) bilirubin. Any abnormality is easily and accurately detected with Ictotest.

COAGULATION STUDIES. The one-stage prothrombin time is prolonged in the presence of severe hepatocellular disease or long-standing biliary obstruction. A return to normal following parenteral vitamin K favors the latter diagnosis. Factors V, VII, IX, and X are all variably depressed in hepatobiliary disorders, but their individual assays are not warranted for ordinary clinical diagnosis.

A low platelet count is often encountered in chronic liver disease when hypersplenism has supervened.

RADIOISOTOPE SCANS OF THE LIVER. Gamma-emitting radioisotopes have been incorporated into a number of test substances which are taken up by the liver. External detectors can estimate the uptake of the isotope and give useful information about liver function[5] and space-occupying lesions.[7]

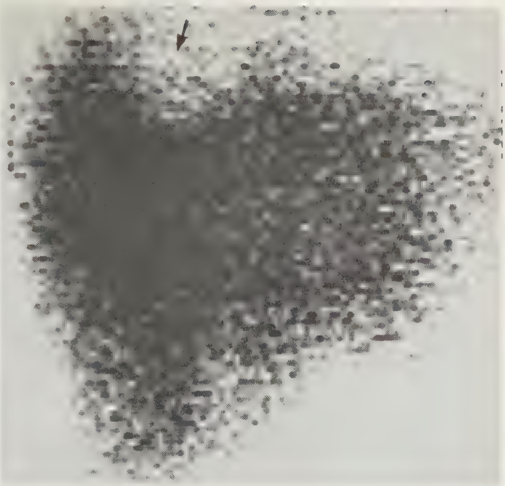

Figure 1. Liver scan of a patient with amebic abscess in the dome of the right lobe of the liver.

1. Radioactivity over the liver is scanned and density plotted on a chart or x-ray film. This technique permits the estimation of liver size and the detection of masses within the liver. Primary or metastatic malignant disease, abscesses, and parasitic cysts have been usefully detected and localized by this means (Figs. 1 and 2). The scan may be repeated in order to follow the response to treatment in these various conditions. Two basically different types of test substances are used for this purpose. Rose bengal-^{131}I is taken up by the parenchymal cells, but its

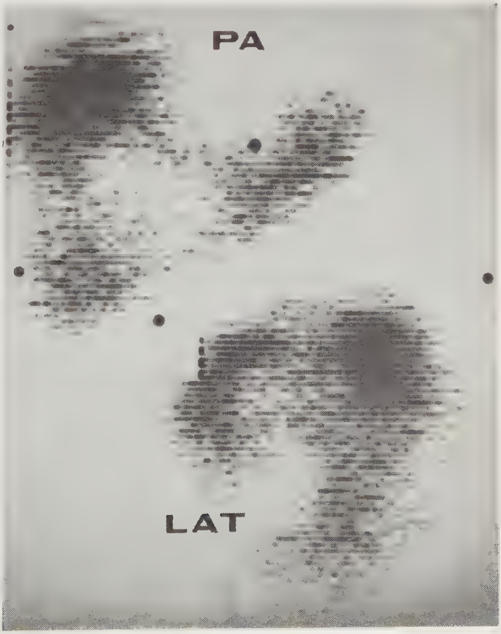

Figure 2. Liver scans (posteroanterior and lateral) in a patient with multiple metastases from carcinoma of the pancreas.

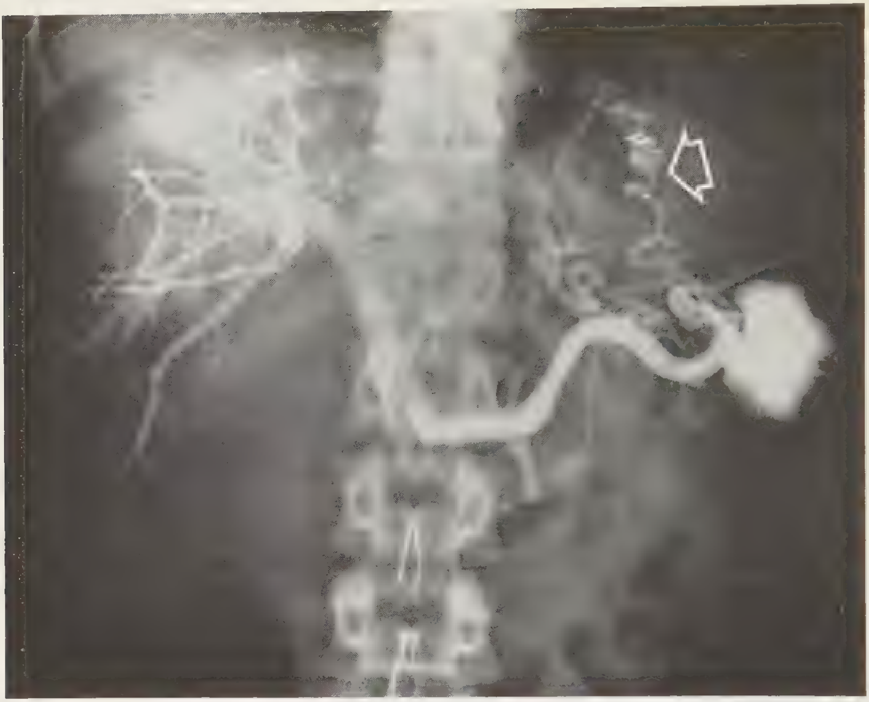

Figure 3. Splenoportogram in a patient with portal hypertension and gastroesophageal varices (arrow).

concentration is impaired in the presence of hepatic dysfunction. Colloidal gold-^{198}Au is taken up by the Kupffer cells and may be used even in the presence of liver cell failure.

2. Liver function can be estimated with radioisotopes by following the time-course of radioactivity in the liver: blood flow, hepatic uptake, and biliary excretion have been estimated differentially by sequential observations of the liver. Rose bengal-^{131}I and vitamin B_{12}-^{60}Co have been used for this purpose. Rather elaborate equipment is necessary and technical problems have prevented the widespread use of these procedures.

RADIOLOGY OF THE BILIARY TREE. A number of procedures are available to allow opacification of the biliary tree in order to detect gallstones or extrahepatic obstruction. When oral and intravenous dye studies fail, the technique of percutaneous transhepatic cholangiography has been employed. It is important that this latter procedure be performed with all the precautions of sterile technique, under fluoroscopic control, and with the anticipation that surgical exploration will be performed within hours if a dilated duct is encountered.

ASSESSMENT OF PORTAL HYPERTENSION. The search for esophageal and gastric varices includes barium swallow, esophagoscopy, and splenoportography with dye injection into the splenic pulp (Fig. 3). Measurements of portal venous pressure can be assayed at the time of splenoportography or through hepatic vein catheterization with measurement of the wedged pressure. Normal portal venous pressure is less than 15 cm. of saline, and significant portal hypertension occurs with levels greater than 20 cm.

NEEDLE BIOPSY OF THE LIVER. Percutaneous liver biopsy has become a well-established procedure; the Menghini "one-second" aspiration biopsy has gradually replaced the Vim-Silverman method in popularity. Liver biopsy[11] is useful in establishing the histologic diagnosis in primary liver disorders, searching for metastatic or diffuse malignant disease, and detecting the hepatic manifestations of a variety of systemic diseases such as tuberculosis. The histologic features of intrahepatic cholestasis often mimic those of extrahepatic biliary obstruction, and thus liver biopsy fails to distinguish between medical and surgical jaundice.

LAPAROTOMY. When other criteria are inconclusive, surgical exploration is often warranted for the diagnosis and treatment of extrahepatic biliary obstruction and a number of other diseases such as tuberculosis, lymphoma, or abscess.

OTHER STUDIES. Special situations call for a number of other studies in the work-up of liver disease. The presence of ascites requires paracentesis in order that the fluids may be examined for protein content, cytology, and specific cultures. Peritoneoscopy[2] is gaining popularity for the direct visualization of the liver, gallbladder, and other intra-abdominal organs, which may be biopsied if necessary. The neurologic evaluation of hepatic coma includes clinical examination as well as an electrocephalogram; this is discussed in a later article (see p. 000). Among the many newer radiologic techniques, catheters may be passed percutaneously and selectively introduced into the hepatic artery or umbilical vein[9] for the injection of dye into the hepatic circulation. A number of serologic abnormalities, including antinuclear antibodies, LE cells, and the various rheumatoid factors, have been noted in chronic active and lupoid hepatitis, juvenile cirrhosis, and primary biliary cirrhosis.[1] The significance of these studies is not yet established, but they have been used in corroboration of some of the above diagnoses.

In the evaluation of terminal liver failure with massive necrosis, severe hypoglycemia, increased levels of serum amino acids, and decreased blood urea nitrogen levels (less than 5 mg. per 100 ml.) have been noted. Marked abnormalities in the clotting mechanism often complicate terminal liver failure. Hemagglutination titers for the detection of viral hepatitis and virus isolation techniques have frequently been reported but not confirmed in clinical practice. This area is one of many where clinical diagnosis in liver disease may be aided by new procedures.

CLASSIFICATION OF LIVER DISEASE

A clinical classification of liver disease, similar to the one introduced for heart disease by the New York Heart Association, has been suggested by Dr. Carroll Leevy.[8] Such an outline would be particularly useful in following the course of chronic liver disease but also serve the purpose of documenting the extent and severity of liver disease at any time.

A. Etiology: nutritional, infectious, neoplastic, etc.
B. Clinical status: graded as follows:
    I. Subclinical
    II. Compensated
    III. Decompensated
    IV. Terminal
C. Biochemical-physiologic status
D. Morphologic changes shown on biopsy

The diagnostic procedures outlined in this article should permit documentation of the type of liver disease present. as well as its status assayed clinically and in the laboratory.

REFERENCES

1. Bouchier, I. A. D., Rhodes, K., and Sherlock, S.: Serologic abnormalities in patients with liver disease. Brit. Med. J., *1*:592, 1964.
2. Caroli, J., and Ricordeau, P.: Value of peritoneoscopy and peritoneoscopic photography in color and of scintillography in the diagnosis of liver diseases. Progress in Liver Disease, *1*:296, 1963.
3. Clermont, R. J., and Chalmers, T. C.: The transaminase tests in liver disease. Medicine, *46*:197, 1967.
4. Davidsohn, I., and Wells, B. B.: Todd-Sanford's Clinical Diagnosis by Laboratory Methods. 13th ed. Philadelphia, W. B. Saunders Co., 1962, pp. 521-577.
5. Englert, E., Jr., Burrows, B. A., and Ingelfinger, F. J.: Differential analysis of the stages of hepatic excretory function with gamma emitting isotopes. J. Lab. Clin. Med., 56:181, 1960.
6. Feinstein, A. R.: Clinical Judgment. Baltimore, Williams & Wilkins Co., 1967.
7. Jones, E. A.: Hepatic scintillography. Gut, 8:418, 1967.
8. Leevy, C. M.: Evaluation of liver function in clinical practice. Indianapolis, The Lilly Research Laboratories, 1965.
9. Piccone, V. A., LeVeen, H. H., White, J. J., Skinner, G. B., and MacLean, L. D.: Transumbilical portal hepatography, a significant adjunct in the investigation of liver disease. Surgery, *61*:333, 1967.
10. Schenker, S., Balint, J., and Schiff, L.: Differential diagnosis of jaundice: Report of prospective study of sixty-one proved cases. Amer. J. Digest. Dis., 7:449, 1962.
11. Sherlock, S.: Needle biopsy of the liver. J. Clin. Path., *15*:291, 1962.
12. Zimmerman, H. J.: Serum enzymes in the diagnosis of hepatic disease. Gastroenterology, *46*:613, 1964.

Veterans Administration Hospital
150 South Huntington Avenue
Boston, Massachusetts 02130

The Differential Diagnosis of Jaundice

HYMAN J. ZIMMERMAN, M.D.*

Confident and accurate diagnosis of jaundice requires an understanding of bilirubin metabolism that permits a rational classification of the types of jaundice and a knowledge of their causes (Table 1). It is also essential to know the relative frequency of clinical manifestations and the sensitivity and reliability of biochemical tests used in differential diagnosis and to avoid dependence on axioms presumed to reflect diagnostic circumstances. Adherence to these principles permits reliable distinction of "medical" from "surgical" jaundice in more than 95 per cent of patients and precise definition of the specific cause of the jaundice in most of these.

BILIRUBIN METABOLISM

A schematic representation of bilirubin metabolism is contained in Figure 1. Senescent erythrocytes are broken down in the reticuloendothelial system, where the liberated hemoglobin is converted to indirect-reacting bilirubin. In the liver, the bilirubin is conjugated with glucuronate to form direct bilirubin, which is excreted into the duodenum. In the intestines, bacteria convert bilirubin through a group of intermediate compounds, to several related substances collectively called "urobilinogen." Most of the urobilinogen is excreted in the feces. An unknown amount is absorbed into the portal blood and re-excreted by the liver.[30] Small amounts of the circulating urobilinogen are excreted in the urine. There is convincing evidence that a fraction (less than 20 per cent) of the urobilinogen is derived from bilirubin in the bone marrow from immature erythrocytes. Very small amounts are presumed to be derived from nonhemoglobin, heme-containing proteins (e.g., catalase) and, perhaps, even from hemoglobin precursor compounds.[1, 28]

It has long been recognized that the nonpolar, indirect bilirubin is poorly soluble in H_2O (Table 2). Consequently, it does not appear in the urine, does not give the direct Van den Bergh (VDB) reaction with the

---

From the Liver and Metabolic Research Laboratory, Veterans Administration Hospital, Washington, D.C., and the Department of Medicine, The George Washington University School of Medicine

*Chief, Medical Service, Veterans Administration Hospital; Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts

Table 1. *Classification of Jaundice and Laboratory Approach to Differential Diagnosis**

		BILIRUBIN TESTS				FLOCCULATION TESTS			SERUM ENZYMES***		
		SERUM BILIR.	URINE								
CATEGORIES	CAUSES†	D/T RATES	BIL.	UROB.	FECES UROB.	T.T.	C.F.	CHOL.** LEVEL	A.P.	GOT	GPT
Prehepatic											
Retention type	Gilbert syndrome Crigler-Najjar syndrome	<0.2	0	N	N	N	N	N	N	N	N
Production type	Hemolysis	<0.2	0	↑	↑ ↑	N	N	N	N	N	N
Hepatic											
Hepatocellular	Viral, toxic hepatitis	0.4-0.6	+	↑	N	↑ ↑ ↑	+	N(↓)	↑ ↑	↑ ↑ ↑ ↑	↑ ↑ ↑ ↑
	Cirrhosis and other chronic forms of parenchymal injury	0.4-0.6	+	↑	N	↑	+	N(↓)	↑	↑ ↑	↑
Hepatocanalicular	Cholestatic form of drug jaundice	0.4-0.6	+	(↓)N(↑)	(↓)	N(↑)	N(+)	↑ ↑ ↑	↑ ↑ ↑	↑ ↑	↑ ↑
	Primary biliary cirrhosis	0.4-0.6	+	N(↑)	(↓)	N(↑)	N(+)	↑ ↑ ↑ ↑	↑ ↑ ↑ ↑	↑ ↑	↑ ↑
Posthepatic	Carcinoma of pancreas or bile ducts	0.4-0.6	+	↓	↓ ↓	N	N	↑ ↑	↑ ↑ ↑	↑ ↑	↑ ↑
	Choledocholithiasis	0.4-0.6	+	(↓)N, ↑	↓	N(↑)	N(+)	↑	↑ ↑	↑ ↑	↑ ↑

* Number of arrows indicate direction, degree and incidence of abnormal results. N indicates normal.

** = See Table 6.

*** = See Figures 3 to 7.

↓ ↓ ↓ ↓, ↑ ↑ ↑ ↑ = Almost all patients show abnormality, many to marked degree.

↑ ↑ ↑ = Almost all patients show abnormality, usually to moderate degree.

↓ ↓, ↑ ↑ = Many patients show abnormality, usually slight to moderate.

↓, ↑ = Many patients show abnormality, usually slight.

(↓), (↑) = Slight abnormality in some of the patients.

† = See text for other causes.

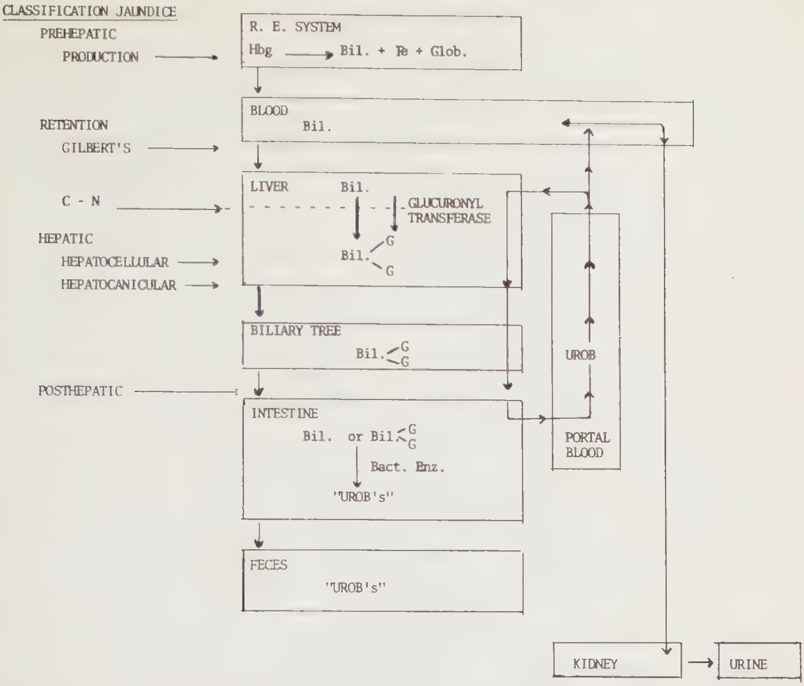

Figure 1. Schematic representation of bilirubin metabolism and indication of presumed or demonstrated site of defect in each category of jaundice (see text for explanation).

water-soluble diazo reagent, and reacts only with the addition of alcohol, which solubilizes both the bilirubin and the reagent. The water-solubility of the polar, direct bilirubin permits its appearance in the urine, and the immediate direct reaction with the VDB reagent.

Direct bilirubin is a diglucuronide of the indirect, conjugated at the proprionic acid side chain. The conjugation occurs in the liver through the action of the microsomal enzyme system, glucuronyl transferase.[35] Recent studies have shown that the direct bilirubin excreted in the bile acids includes small amounts of other conjugates in addition to the glucuronide.[15] These also give the direct reaction with the VDB reagent.

Table 2. *Comparison of Properties of Direct and Indirect Bilirubin*

	DIRECT (CONJUGATED)	INDIRECT (UNCONJUGATED)
Structure	Bilirubin diglucuronide	Bilirubin
Type of compound	Polar	Nonpolar
Solubility		
Water	+	−
Alcohol	+	+
Van den Bergh reaction	Direct	Indirect
Presence in urine	+	−

CLASSIFICATION OF JAUNDICE

The type of defect in bilirubin metabolism that is uncovered by analysis of bile pigments in the excreta and serum serves as the basis for the Ducci[13] classification of jaundice as prehepatic, hepatic, or posthepatic (Table 1) and permits an approach to the differential diagnosis. *Prehepatic* jaundice is characterized by elevated serum levels of unconjugated bilirubin. It results from deficient ability to remove bilirubin from the blood (retention jaundice) or from production of bilirubin (hemolysis) exceeding normal removal capacity. Since the increased serum bilirubin is mainly indirect, there is no bilirubin in the urine. Fecal and urine urobilinogen levels are normal or low in *retention* jaundice and elevated in *production* jaundice.

In *hepatic* and *posthepatic* jaundice, there are elevated serum levels of conjugated bilirubin because of defective excretion into the canaliculus or of "regurgitation" into the blood, as well as retention of unconjugated bilirubin. Hepatic jaundice may be considered to include two types, one characteristic of parenchymal hepatic injury (hepatocellular); the other (hepatocanalicular) resembles posthepatic jaundice. In *hepatocellular* jaundice, the urine usually contains increased urobilinogen and bilirubin (in viral hepatitis this may occur during only part of the course of the illness); and fecal urobilinogen is normal or only slightly decreased. In posthepatic jaundice due to carcinoma of the pancreas ("complete" obstruction), the fecal and urine content of urobilinogen is low. In "incomplete" *posthepatic* jaundice (choledocholithiasis or common duct tumors) and in *hepatocanalicular* jaundice, urine urobilinogen levels also may be low; more often they are normal or even increased and the fecal urobilinogen content is not as low as that of complete posthepatic jaundice.

For each type of jaundice, there are several causes, both acquired and genetic. Precise diagnosis depends on an awareness of the various types of jaundice and the multiple causes of each.

Prehepatic Jaundice

Retention jaundice includes several genetic entities. *Gilbert's syndrome* (constitutional hepatic dysfunction, hereditary nonhemolytic jaundice, icterus intermittens juvenalis) is a benign condition, characterized by slight elevation (2 to 8 mg. per 100 ml.) of the serum level of bilirubin, almost all of it unconjugated. Symptoms are negligible and when present are probably iatrogenic. The defect in some cases that have been studied has been inferred to be in the transport of bilirubin from sinusoidal blood into the hepatocyte.[6] A mendelian dominant type of inheritance for the entity has been proposed. It is probable, however, that "Gilbert's syndrome" has included several other entities.[1, 28, 38] At least one of these represents a mild, compensated hemolytic state. Another form may represent a relatively slight defect in bilirubin-conjugating ability.[1] Some instances of Gilbert's syndrome probably represent hyperbilirubinemia acquired as a residual of viral hepatitis. Without careful genetic and other studies, these several forms cannot be distinguished from the genetic defect in bilirubin removal. The *Crigler-Najjar* *syndrome* is a rare but well-known and well-studied form of retention jaundice first described 16 years ago.[9] The result of deficient hepatic glucuronyl transferase activity,[35] it is characterized by very high levels of unconjugated bilirubin (20 to 40 mg. per 100 ml.), resultant neurologic damage and usually early death. It is transmitted as a mendelian recessive. A similar defect is found in the Gunn rat.[35]

Two other syndromes of retention jaundice due to defective bilirubin conjugation occur in infants. One, the *Lucey-Driscoll* syndrome, is apparently the result of an unidentified factor, presumably a steroid in maternal blood transmitted to the infant.[1] The other is a form of prolonged, severe unconjugated hyperbilirubinemia in infants nursed by mothers whose milk contains pregnane-3(alpha),20(beta)-diol. This steroid can inhibit glucuronyl transferase activity.[1] A transitory defect in bilirubin conjugation also is seen in immature infants.[1, 35]

Production jaundice is caused by the genetic or acquired forms of hemolysis. The increased rate of bilirubin formation leads to increased levels of fecal and usually of urine urobilinogen. Bilirubin is not found in the urine in "pure" production jaundice. Some hemolytic states, however, produce secondary liver damage (e.g., sickle cell disease) or have associated liver disease (e.g., Zieve syndrome)[13] and may, accordingly, have significantly elevated serum levels of conjugated bilirubin and a resultant bilirubinuria.

A special form of the production type of prehepatic jaundice is the "shunt" hyperbilirubinemia of Israels et al.[24] In this genetic syndrome, increased amounts of bilirubin are formed from sources other than circulating erythrocytes, presumably[1] immature erythrocytes in the marrow.

Hepatic Jaundice

In both the hepatocellular and hepatocanalicular types of hepatic jaundice, the levels of conjugated and unconjugated bilirubin are elevated. The hepatocellular type, which is the result of parenchymal hepatic injury, leads to jaundice by an unknown mechanism, perhaps reversal of the normal polarity of the hepatocyte, permitting regurgitation of conjugated bilirubin into the blood after it has been conjugated.[28] Disturbances in pigment metabolism differ from those of posthepatic jaundice only in degree. Thus, the ratio of direct to total (D/T ratio) bilirubin of the serum resembles that of obstructive jaundice, and there is bilirubin in the urine. However, levels of fecal urobilinogen are usually not below normal, and those of urine urobilinogen may be increased, presumably because the diseased liver is unable to clear normally the urobilinogen returned from the bowel. Disease that produces injury of the hepatic parenchyma can cause hepatocellular jaundice. These include viral hepatitis, some forms of drug-induced and other chemical hepatic injuries,[16] alcoholic steatonecrosis,[17] and active postnecrotic cirrhosis.

Hepatocanalicular jaundice ("intrahepatic cholestasis," "cholangiolitic hepatitis") is a form of intrahepatic disease that can mimic posthepatic (obstructive) jaundice.[13] In this type of hepatic disease, the parenchyma is usually structurally normal or almost normal, and the chief apparent defect is failure to excrete bilirubin normally. The disturbance in pigment metabolism resembles in all important aspects that of posthepatic jaundice, and the clinical features of patients with hepatocanalicular jaundice also resemble those of obstructuve jaundice. Indeed, these two forms of jaundice are difficult to distinguish and they may be categorized as cholestatic jaundice, intrahepatic and extrahepatic, respectively.[36] Hepatocanalicular jaundice can be the result of genetic or acquired disease.[23]

Genetic forms of hepatocanalicular jaundice include the *Dubin-Johnson* syndrome, the *Rotor* syndrome, "*benign, recurrent familial cholestasis*" and probably *cholestatic jaundice of pregnancy.* The Dubin-Johnson and the Rotor syndromes are similar.[36] Both are characterized by persistently elevated levels of bilirubin, much of it conjugated. In these entities, the ability to clear unconjugated bilirubin from the blood, store it, and conjugate it, is apparently normal, but the ability to transport the conjugated bilirubin across the canalicular membrane is apparently defective.[1] The unimpaired ability to remove foreign dyes from the sinusoidal blood and to store them in the hepatocytes, coupled with an impaired ability to excrete them, accounts for a characteristic pattern of BSP retention. When the dye excretion test is performed, the blood level of BSP measured at the standard interval of 45 minutes may be normal or only slightly abnormal. The level an hour or two later is much higher as the result of regurgitation into the blood of stored but unexcreted dye.[31] In the Dubin-Johnson syndrome, the centrolobular cells of the liver contain a melanin-like pigment,[12] while the liver of patients with the Rotor syndrome contains no such pigment.[5] Most cases of the Dubin-Johnson syndrome are unable to excrete and concentrate iodopanic acid sufficiently to visualize the gallbladder, a defect apparently not observed in the Rotor syndrome. Nevertheless, the possibility that the Rotor syndrome is a variant of the Dubin-Johnson, rather than a separate entity, remains under consideration.

Cholestatic jaundice of pregnancy is a benign condition which occurs late in gestation, subsides immediately after delivery, and often recurs in successive pregnancies.[11] The physiologic defect in the excretion of bilirubin resembles that of the Dubin-Johnson syndrome. A number of the reported cases appear to have a genetic basis.[11] Patients who have this syndrome are more prone than other women to develop jaundice while taking contraceptive steroids.

A rare form of familial cholestatic jaundice, that appears to be genetic, has been described as "*benign familial recurrent cholestasis*."[37] This syndrome is clearly distinguishable from the Dubin-Johnson syndrome by the occurrence of episodic rather than of sustained jaundice, the greater depth of jaundice during the episodes, and the normal excretion of dye between attacks.

There are a number of *acquired* forms of intrahepatic cholestasis.[23, 36] Most common are instances due to adverse reactions to *drugs* (chlorpromazine, erythromycin estolate, organic arsenicals, C-17 alkylated steroids). Rare and probably of exaggerated importance as a cause of the syndrome is viral hepatitis, although cholestatic forms do occur.[11]

Instances of cholestatic jaundice that appear to be idiopathic are described. Some are probably the result of ingestion of a drug that has been overlooked. Instances of cholestatic jaundice occur as a benign postoperative syndrome of unknown mechanism.[25] Infants with gram-negative infection (especially E. coli infections) can develop cholestatic jaundice.[16]

Primary biliary cirrhosis is a form of chronic intrahepatic cholestasis observed mainly in females.[36] It is idiopathic and perhaps due to autoimmune processes. An identical syndrome has been reported as a sequel to drug-induced cholestasis (chlorpromazine and organic arsenical-induced jaundice) in a few patients.[10] A syndrome that resembles primary biliary cirrhosis has been reported in patients with postnecrotic cirrhosis,[36] in a few with sarcoidosis,[20] in some with ulcerative colitis,[39] and in sclerosing cholangitis.[36]

Severe *fatty metamorphosis* in *alcoholics* has been described as a cause of cholestasis.[3] It is the opinion of the author, however, that fatty liver per se rarely causes a significant degree of jaundice. Alcoholics with jaundice usually have *steatonecrosis* (fatty liver with necrosis and Mallory bodies), which leads to hepatocellular jaundice.[17] Some alcoholic patients present with posthepatic jaundice due to obstruction by pancreatitis or a pancreatic pseudocyst.[12] Others may have hemolytic jaundice of the Zieve syndrome.[43] In some alcoholic patients, biopsy may reveal steatonecrosis, blood studies may demonstrate hemolysis, and other features may indicate pancreatitis, to suggest that all three elements may be contributing to jaundice.

Posthepatic Jaundice

Most cases of obstructive jaundice are the result of a carcinoma of the head of the pancreas or of choledocholithiasis. Tumors of the common duct are an uncommon cause. Benign lesions of the pancreas (pseudocyst, pancreatitis), as a cause, have been cited above. Infiltrative hepatic lesions (lymphoma, carcinoma) rarely can compress the biliary tree intrahepatically and lead to posthepatic jaundice or by producing hepatic necrosis, lead to hepatocellular jaundice.[12, 36] More often these infiltrative lesions lead to only slight hyperbilirubinemia and rarely to icterus. Instances of a syndrome of intrahepatic cholestasis have been described in patients with Hodgkin's disease, even when there is no demonstrable infiltration of the liver by neoplastic tissue.[36]

DIAGNOSTIC PROCESS

The process of arriving at the correct diagnosis of the cause of jaundice incorporates the clinical impression, biochemical testing, special procedures, and attempts to relate these separate facets, one to the other. It may be considered to include four steps. (1) The *diagnostic posture* of the clinician is determined by the age, sex, history of illness, and other circumstances surrounding the development of jaundice. (2) *Clues* from the *physical examination* and results of the *hemogram* may support and extend the initial impression. (3) *Biochemical studies* directed at

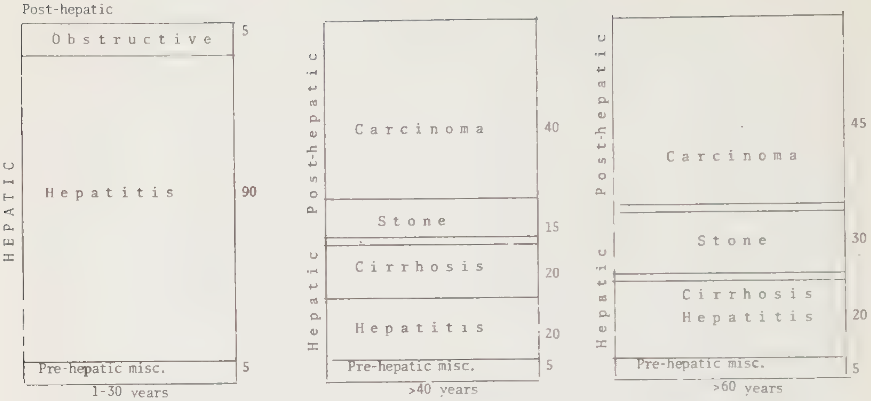

Figure 2. Relative incidence of causes of jaundice by age groups.

the differential diagnosis of jaundice, correlated with the clinical features, permit a tentative or reasonably certain distinction of medical from surgical jaundice, and often a specific diagnosis. (4) Repetition of these studies, during a brief *period of observation*, interpreted in the light of the evolving clinical features and aided by *special procedures*, serves to confirm the diagnosis in most instances.

Diagnostic Posture

An orientation toward the diagnosis derives from the anamnesis and the findings on physical examination. Descriptions by the patient of changes in the color of the excreta, though time-honored clinical clues, offer little significant assistance. The "clay-colored stool," though characteristic of obstructive jaundice, can also be seen in hepatocellular jaundice, if the jaundice is deep.

Age, mode of onset, and possible exposure to specific etiologic circumstances help to direct attention to the probable diagnosis. Immediate bias derives from the age of the patient (Fig. 2). Approximately 90 per cent of jaundiced patients under the age of 30 (and beyond infancy) have viral hepatitis.[11] The remainder may have hemolytic jaundice, one of the types of hereditary hyperbilirubinemia, or toxic hepatopathy. Infectious hepatitis is less frequent beyond this age, but serum and toxic hepatitis may occur at any age. Choledocholithiasis and carcinoma of the pancreas or biliary tree become important causes of jaundice beyond the age of 40. The icterus of three quarters of the patients beyond age 60 results from anatomical obstruction of the biliary tree. Even in these elderly patients, however, carcinoma accounts for only half of the cases of jaundice. One fourth are caused by choledocholithiasis and the remainder by cirrhosis, serum hepatitis, or drugs.[22] Clearly, the relative incidence of the various entities depends on the type of hospital and its patient population.

Slight additional bias derives from knowledge of occupation, habits, and other opportunities for exposure to agents that may produce hepatic disease. These may include contact with other jaundiced patients; ingestion of raw or steamed sea food or unsafe water; recent administration of blood, plasma or other biologic products or of parenteral medications, even including local anesthetics given by the dentist; or occupations such as nursing, laboratory technology, or work in dialysis units that afford percutaneous exposure to contaminated equipment, blood, or tissues. Alcoholism is, of course, relevant to the possible diagnosis of the stage of cirrhosis (steatonecrosis) that may be responsible for jaundice. In the patient with acute hepatic and renal disease, efforts should be made to elicit a history of occupational or domestic exposure to halogenated hydrocarbons or of exposure to rats or dogs that might be the means for acquiring leptospirosis (a rare diagnosis in our experience). Careful inquiry regarding exposure to one of the ever mounting list of drugs known to be hepatotoxic[14] is, of course, necessary. Recent operations may be relevant with respect to the possibility of benign postoperative cholestatic jaundice[25] or of anesthetic-induced (halothane?) hepatic injury.[18]

MODE OF ONSET. An abrupt onset (Table 3) orients diagnostic attention to viral hepatitis, drug-induced jaundice, or choledocholithiasis, whereas chronic insidiously developing jaundice, of course, suggests the diagnosis of carcinoma or cirrhosis. An illness that begins with a shaking chill is unlikely to be viral hepatitis. Chilliness is common, but frank, shaking chills are very rare in this condition. Chills are frequent in gallstone obstruction and may occur in leptospirosis and infectious mononucleosis. Repeated episodes of chills followed by jaundice, of course,

Table 3. *Differential Diagnosis of the Most Common Causes of Jaundice by History*

	HEPATITIS	ALCOHOLIC STEATONECROSIS*	DRUG-INDUCED	CHOLEDOCHOLITHIASIS	CA. OF PANCREAS
Onset: Acute	+	±	+	+	−
Chronic	−	+	±	±	+
Fever	Pre	During	Pre or During	Pre, During	−
Chills	−	−	±	+	−
Chilliness	Pre	−	±	+	−
Pain	±	±	±	+++	+
Weight loss	−	±	−	±	+
Anorexia	+	±	±	±	−
Fatigue	+	±	±	−	−
Rash	−	−	±	−	−
Itching	±	−	+	±	+

* Refers to jaundiced stage of Laennec's cirrhosis.
Pre = Only during preicteric stage.
During = With jaundice.
± = Rare.
+ = Present.
− = Absent.

are strongly suggestive of common duct calculi. Fever *prior* to jaundice may occur in viral or toxic hepatitis or gallstone obstruction, but fever that persists *after* jaundice has appeared is rare in viral hepatitis and infrequent in drug-induced jaundice. Fever is usual in choledocholithiasis and in the cirrhotic with jaundice. Clearly of diagnostic significance for the recognition of viral hepatitis is the *abrupt* onset of anorexia and nausea. Distaste for cigarettes often accompanies the anorexia.

PAIN. The high frequency of the acute pain of gallstone obstruction, the distinct incidence of chronic, dull boring pain of carcinoma of the pancreas, the occasional abdominal pain of some types of drug hepatotoxicity, and the infrequency of true pain in viral hepatitis, are all useful in providing diagnostic orientation. It is a common misconception that viral hepatitis is accompanied by prominent abdominal pain. Patients with this disease complain of a dull, dragging epigastric or right upper quadrant discomfort or a feeling of fullness. They dislike supporting the weight of a book or the examiner's hand on the epigastrium, and react to such experiences with nausea and queasiness, but frank pain is rare in viral hepatitis.

Clues from Physical Examination

The evidence obtained from physical examination is of limited but definite usefulness (Table 4). The pale yellow of hemolytic icterus, orange hue of deep hepatocellular jaundice, and greenish tint of posthepatic jaundice are relatively unhelpful, time-worn clues. The type and degree of hepatomegaly is of some importance. It is usual for the liver to be felt with difficulty in viral hepatitis. When it is palpable, the edge is usually not sharp. A readily palpated, firm liver suggests chronic

Table 4. *Differential Diagnosis of the Most Common Causes of Jaundice by Physical Examination and Routine Laboratory Data*

	HEPATITIS	ALCOHOLIC STEATONECROSIS*	DRUG-INDUCED	CHOLEDOCHOLITHIASIS	CA.
Skin					
Spider nevi	–	+	–	–	–
Abdominal venous pattern	–	+	–	–	–
Xanthomas	–	–	±	±	±
Fetor hepaticus	±	±	–	–	–
Firm liver	–	+	±	±	+
Encephalopathy	±	±	–	–	±
Splenomegaly	±	+	±	±	±
Palpable gallbladder	±	±	–	–	–
Routine lab.					
Leukopenia	±	–	–	–	–
Leukocytosis	–	+	–	±	±
Anemia	–	+	–	±	±
Eosinophilia	–	–	+	–	–

*Refers to jaundiced stage of Laennec's cirrhosis.
± = Rare.
± = Present.
– = Absent.

disease rather than acute hepatitis. An enlarged, firm liver is to be expected in patients with cirrhosis. Hepatomegaly also is found in most patients with posthepatic jaundice. Indeed, absence of hepatomegaly should make one doubt the latter diagnosis. It is axiomatic that the stony hard liver is suggestive of metastatic carcinoma, but this is a rare cause of deep jaundice.

An enlarged gallbladder is less frequently present in patients with the jaundice of carcinoma of the pancreas than is implicit in the traditional emphasis on the diagnostic value of the Courvoisier sign. Conversely, even patients with benign jaundice produced by stones in the common duct or by viral hepatitis may have a coincidental gallstone in the cystic duct, leading to an enlarged gallbladder. Generally, the gallbladder which is distended because of a stone in the cystic duct is tender, while the enlarged gallbladder of Courvoisier is not tender.

A palpably enlarged spleen in the jaundiced patient suggests that the jaundice might be due to cirrhosis, infectious mononucleosis, or lymphoma, and less commonly to viral hepatitis, although slight splenomegaly occurs in 10 to 20 per cent of patients with hepatitis. Splenomegaly may be demonstrable in patients with a carcinoma of the body of the pancreas with secondary obstruction of the splenic vein. Recognition of the spider nevi and collateral venous pattern of cirrhosis, of the fetor hepaticus of parenchymal hepatic failure, and of the xanthomas of biliary cirrhosis is, of course, important.

Analysis of the hemogram also provides clinical clues. Leukocytosis offers strong evidence against the diagnosis of viral hepatitis. Levels above 10,000 are rare in this condition, while leukocytosis is usual in the alcoholic with steatonecrosis, and in choledocholithiasis. Changes in the hematocrit or hemoglobin levels are of assistance in the recognition of the production type of prehepatic jaundice. Eosinophilia is a useful clue to some types of drug-induced jaundice.

Biochemical Tests

In many patients, the clinical clues establish an orientation toward the most probable diagnosis, but do not permit a specific diagnosis. To confirm or establish the cause of the jaundice, a few well-known laboratory measures are necessary (Table 7).

Many tests have been recommended (Table 5). Most useful are the tests based on bilirubin metabolism: measurement of the serum levels of alkaline phosphatase and of the two transaminases (GOT and GPT), of cholesterol, and of the prothrombin time (before and after vitamin K administration). Of ancillary help are the levels of serum proteins and their fractionation and the values for the flocculation tests. The results obtained with these tests in most patients with acute hepatocellular jaundice differ reliably from those in most patients with posthepatic jaundice (Table 5). There are, however, four main patterns provided by these tests. One is characteristic of acute hepatocellular jaundice (hepatitis); another reflects chronic hepatocellular jaundice (cirrhosis). A third is characteristic of complete posthepatic jaundice (carcinoma of the pancreas) and of hepatocanalicular jaundice, and a fourth of in-

Table 5. *Role of Biochemical Tests and Other Procedures in Differentiation Between Hepatic and Posthepatic Jaundice*

IMPORTANTLY USEFUL	USEFUL AS SUPPLEMENTARY PROCEDURES	NOT HELPFUL, REDUNDANT OR STILL INVESTIGATIVE
Serum bilirubin (direct and total)	Fecal urobilinogen	Serum levels of vitamin B_{12} and iron
Urine urobilinogen	Serum proteins and electrophoresis	Serum bile acids
Urine bilirubin	Thymol turbidity	Ratio trihydroxy to dihydroxy bile acids
Alkaline phosphatase	Cephalin flocculation	Cholesterol esters
GOT	LDH	
GPT		
Prothrombin time and response to vitamin K		
Cholesterol level		
Liver biopsy	Duodenal drainage	Rose bengal-^{131}I (uptake by liver and pattern of excretion)
	Transhepatic cholangiography and other radiographic studies	Triolein-^{131}I absorption
		Effect of steroids on jaundice

complete posthepatic jaundice (choledocholithiasis) (Table 1).

TESTS BASED ON BILIRUBIN METABOLISM. The tests for urine bilirubin and urobilinogen are time-honored and essential procedures for a rational approach to the differential diagnosis of jaundice. Fecal urobilinogen determination, however, is usually reserved for the demonstration of hemolytic jaundice. Levels above 300 mg. per 24 hours (or 400 Erlich units in a "catch" specimen) are considered evidence of bilirubin overproduction, but this should be confirmed by other studies for hemolysis. Few clinics today utilize the difficult, quantitative fecal urobilinogen analysis for the distinction of hepatic from posthepatic jaundice.

The partition of serum bilirubin into direct (conjugated) and indirect (unconjugated) fractions is of limited diagnostic value. A ratio of direct to total bilirubin (D/T) of less than 0.2 indicates that the jaundice is probably prehepatic. A ratio between 0.2 and 0.4 may be found in hepatocellular jaundice, or in that caused by combined mechanisms (e.g., sickle cell anemia with hemolysis and hepatocellular damage). Values for the ratio above 0.4 may occur in both types of hepatic and in posthepatic jaundice.[45]

SERUM ENZYME LEVELS. Serum levels of alkaline phosphatase (AP) and of the two transaminases (GOT and GPT) provide a simple battery of enzyme tests useful in the differential diagnosis of jaundice[46] (Fig. 3). Alkaline phosphatase levels are relatively slightly elevated in hepatocellular jaundice (hepatitis, cirrhosis) and moderately or markedly elevated in patients with posthepatic and hepatocanalicular jaundice. Values are more variable in the "incomplete" obstructive jaundice of choledocholithiasis than in the "complete" obstruction of carcinoma of the pancreas. Values for the transaminases in acute hepatocellular jaundice are generally higher than those of patients with chronic forms (cirrhosis) and than those of patients with posthepatic or hepatocanalicular jaundice. Values for lactic dehydrogenase (LD) are only slightly elevated in both hepatic and hepatocanalicular jaundice, but may be of help in special circumstances (vide infra).

Alkaline phosphatase levels in most patients with the complete obstructive jaundice of carcinoma of the head of the pancreas range from 15 to 40 Bodansky Units (BU) and are often above 25 units (Fig. 4). Values are often lower in the incomplete obstructive jaundice produced by gallstones or common duct tumors. About 30 per cent of these patients have values below 15 BU.[46]

Levels of serum alkaline phosphatase also are usually relatively slightly increased in hepatocellular jaundice. Approximately 90 per cent of patients with viral hepatitis or with toxic hepatocellular jaundice have elevated serum alkaline phosphatase values, but 95 per cent of these are below 15 Bodansky units (BU). Levels in patients with postnecrotic cirrhosis are usually even lower. It is well known that patients with acute hepatocanalicular jaundice or with primary biliary cirrhosis have values as high as or higher than those observed in patients with posthepatic jaundice.

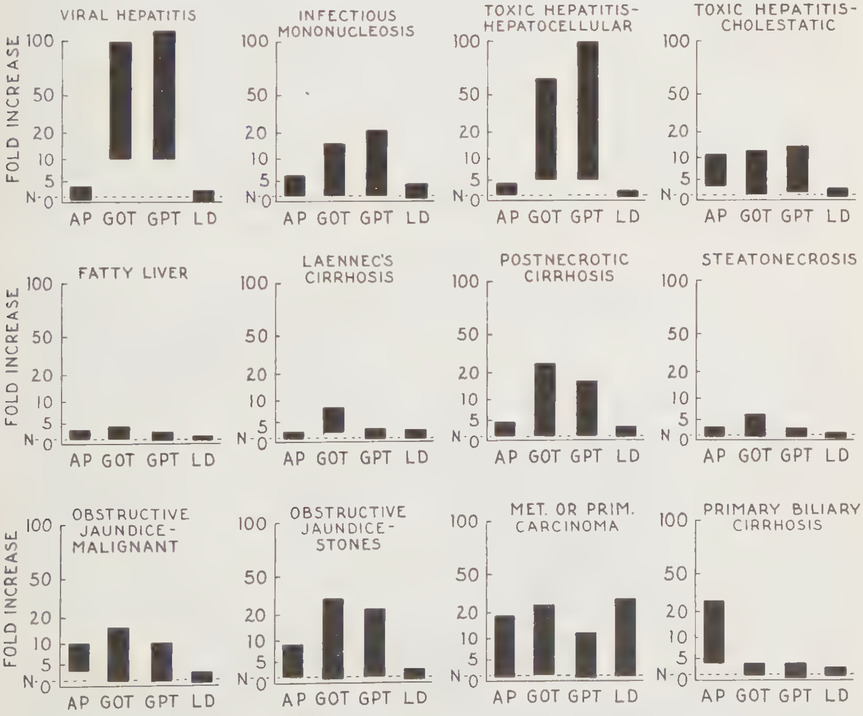

Figure 3. Patterns of abnormality of small battery of enzymes observed in various types of hepatic disease (see text for meaning of abbreviations).

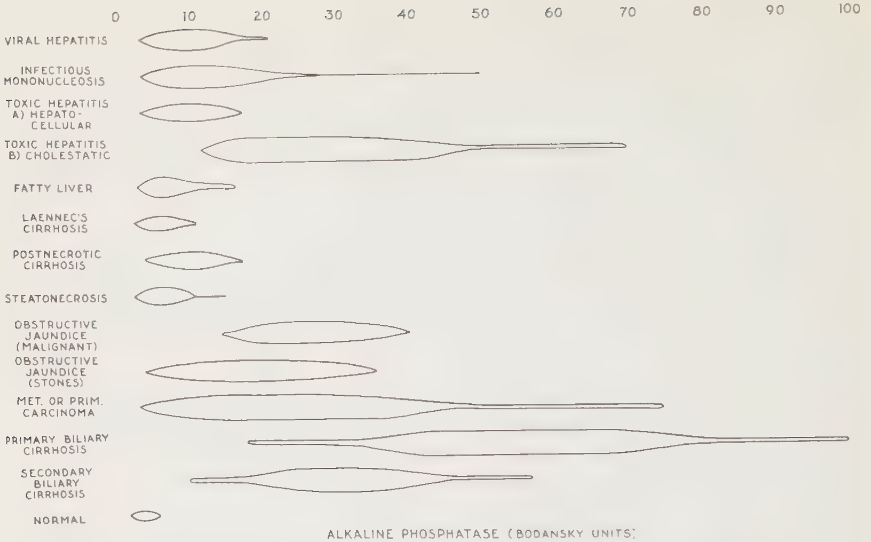

Figure 4. Schematic representation of range of values for alkaline phosphatase in various hepatic diseases.

Glutamic oxaloacetic transaminase (GOT) levels are also of distinct value in the differential diagnosis of jaundice[16] (Fig. 5). The highest levels are observed in patients with hepatocellular jaundice. In a jaundiced patient, the values above 300 units suggest the diagnosis of acute, viral, or toxic hepatitis, since obstructive jaundice, cirrhosis, and metastatic carcinoma usually are associated with much lower levels of this serum enzyme (below 300 units). In acute viral hepatitis, the levels range from 300 to 4000 units early in the illness, but drop to a nondiagnostic range (below 300 units) by the end of the first or second week of

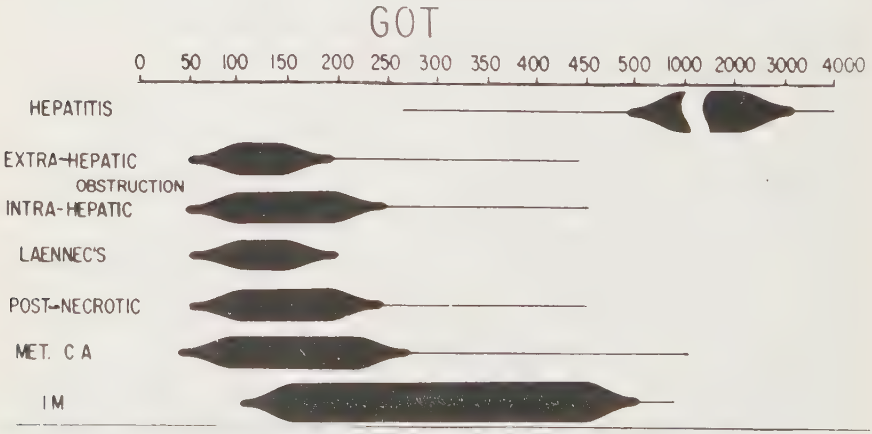

Figure 5. Schematic representation of values for GOT in various forms of hepatic disease. "Hepatitis" refers to acute viral hepatitis or to drug-induced acute hepatocellular jaundice. "Intrahepatic" refers to intrahepatic cholestasis, drug-induced or idiopathic. Met. Ca. refers to metastatic carcinoma and I. M. refers to infectious mononucleosis.

the disease. Values in the obstructive jaundice of choledocholiathiasis occasionally reach values (300 to 1000 units) suggestive of hepatitis. This presumably reflects the hepatic injury secondary to ascending cholangitis. Even higher values may occur in patients who sustain bacteremic shock, since shock of any origin can lead to high levels of GOT.

Glutamic pyruvic transaminase (GPT) levels are higher than those of GOT in about two thirds of the patients with hepatitis, in most patients with infectious mononucleosis, and in some patients with hepatocanalicular jaundice. In cirrhosis and metatastic carcinoma and in nonhepatic disease (myocardial infarction, muscle disease) the GPT level is almost always lower than the GOT value. In posthepatic jaundice, the two are almost equal.[46]

Combining the values for the two transaminases (Fig. 6) permits recognition of a number of diagnostically helpful zones. High values for GOT (>500 units) with a GPT value as high or higher (GOT/GPT ratio <1.2) are almost diagnostic of acute viral or toxic hepatitis. Relatively slightly elevated values (<300 units) with GPT values approximately equally elevated are consistent with the diagnosis of obstructive jaundice or may represent a subsiding hepatitis. Values for GOT in the intermediate range (300 to 500 units) with a GOT/GPT ratio below 1.2 are more characteristic of hepatitis than of obstructive jaundice, but can be seen in the latter. In Laennec's cirrhosis, the relatively low values for GOT and high GOT/GPT ratio (>1.5) are characteristic. In active postnecrotic cirrhosis and in chronic active hepatitis, the transaminase values may resemble those of Laennec's cirrhosis or those of subsiding hepatitis.

Lactic dehydrogenase (LD) levels [16] are elevated in a variety of conditions (myocardial and pulmonary infarction, muscle disease, carcinoma, and other neoplastic or other proliferative hematologic lesions).

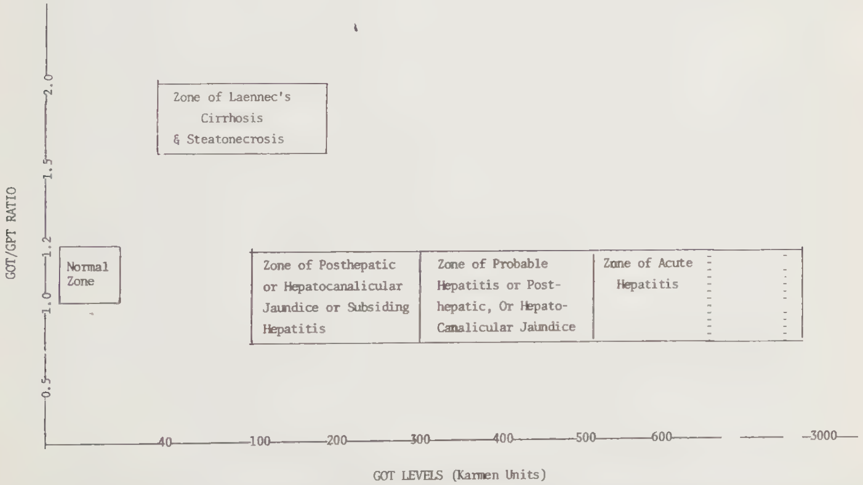

Figure 6. Relationship between GOT/GPT ratio and GOT levels in several forms of jaundice. Note high value for ratio for GOT in steatonecrosis, and low values for ratio in posthepatic jaundice and acute hepatitis.

Table 6. *Serum Cholesterol Levels in the Most Common Causes of Jaundice*

TYPE AND CAUSE OF JAUNDICE	CHOLESTEROL LEVEL	
	TOTAL	ESTERS
Hepatic		
Hepatocellular		
Hepatitis (acute)	↓ ↓	↓ ↓
(mild)	N	↓
Cirrhosis (Laennec's)	N(↓)(↑)	↓
(postnecrotic, active)	↓	↓ ↓
Hepatocanalicular (acute)	↑ ↑ ↑	↓
Biliary cirrhosis (primary)	↑ ↑ ↑	↓
Posthepatic		
Complete	↑ ↑	↓
Incomplete	↑	↓

The values for LD are normal or only slightly elevated in patients with benign posthepatic jaundice, hepatitis, or cirrhosis. Despite the apparent nonspecificity of this measurement, patients with posthepatic jaundice who have high LD levels should be suspected of neoplastic obstruction of the biliary tree with extensive metastases to other sites, or of metastatic carcinoma of the liver obstructing the common hepatic duct.

Characteristic abnormalities of the serum *aldolase, phosphohexoisomerase, malic dehydrogenase, leucine aminopeptidase, 5′-nucleotidase, ornithine carbamyl transferase, cholinesterase*, and other serum enzymes have been demonstrated in patients with hepatobiliary disease, but determination of these levels adds little to the diagnostic use of the patterns of abnormality (Fig. 3) provided by the two transaminases, alkaline phosphatase and lactic dehydrogenase.[46]

CHOLESTEROL LEVELS (Table 6). The hypercholesterolemia of posthepatic jaundice and the hypocholesterolemia of hepatocellular disease have long been considered diagnostically useful features.[31] The depression of the level of cholesterol, however, which occurs in hepatic parenchymal failure is a late phenomenon which adds little to the clinical appraisal. Furthermore, the depression of the serum level of cholesterol esters, at one time advocated as a useful test for differential diagnosis of jaundice, is of little clinical usefulness. Some depression of the fraction of the esterfied cholesterol occurs in both extrahepatic and obstructive jaundice and in intrinsic hepatic disease. The most marked degree of depression occurs in advanced hepatic disease, but in this setting adds little to the diagnosis which is readily apparent by many other means. However, the demonstration of the degree of hypercholesterolemia associated with posthepatic and hepatocanalicular jaundice is diagnostically useful. Patients with posthepatic jaundice due to carcinoma have moderately elevated levels of cholesterol, usually 300 to 500 mg. per 100 ml. Patients with posthepatic jaundice due to choledocholithiasis tend to have somewhat lower but still elevated levels. Patients with acute intrahepatic cholestasis (hepatocanalicular jaundice) usually have levels that may be even higher. The highest levels are observed in patients with chronic intrahepatic cholestasis (primary biliary cirrhosis).

PLASMA COAGULATION FACTORS. Decreased levels of a number of clotting factors occur in patients with hepatobiliary disease,[10] Only the depressed prothrombin concentration and characteristic response to vitamin K administration in obstructive jaundice, but with a negligible response in hepatocellular jaundice, has found diagnostic application. This is a useful test, but application of it is limited by the occurrence of hypoprothrombinemia in only 25 per cent of patients with posthepatic jaundice.

SERUM PROTEIN LEVELS. Measurement of serum protein levels is of ancillary value in the differential diagnosis of jaundice.[19, 44] The abnormalities observed are usually characteristic for various diseases (Table 7), although not specific. A pattern of abnormality of the serum proteins consistent with the working diagnosis that is arrived at by other means, is reassuring, but a pattern out of keeping with the diagnosis that is suggested by other data should lead to a reappraisal of the problem, not necessarily a change of diagnosis.

Hepatic parenchymal disease is likely to produce depression of the levels of albumin, mucoprotein, and haptoglobin and elevation of the levels of gamma globulin, often accompanied by slight elevation of the beta globulin values.[11] Obstruction of the biliary tree, however, is more likely to produce elevated levels of lipoproteins (alpha-2 and beta globulins) and normal or slightly elevated levels of mucoproteins and haptoglobin.[41] However, some distinction must be drawn between the effects of acute and chronic hepatic disease, and of the several forms of obstructive jaundice, on these protein fractions.

Hypoalbuminemia is usual in Laennec's or postnecrotic cirrhosis, but is absent or slight in most patients with acute viral or toxic hepatitis. Depression of the albumin level is also slight in most patients with posthepatic or hepatocanalicular jaundice. Slightly elevated levels of the total globulin and of the gamma globulin level occur in approximately half of the patients with acute viral hepatitis, usually several weeks after onset. Elevation of the globulin level is moderate in Laennec's cirrhosis, usually below 4.5 gm. per 100 ml., and the gamma globulin level is usually less than 35 per cent of the total protein value. In the electrophoretogram, "fusion" of the beta and gamma peaks may be seen. In active postnecrotic cirrhosis, the total globulin and gamma globulin levels may be higher and the electrophoretic pattern does not show beta-gamma "fusion."[19] The total globulin and gamma globulin levels are normal or relatively slightly increased in most patients with obstruction of the biliary tree, although occasionally high values for globulin may be seen in posthepatic jaundice. Serum levels of *mucoproteins* and of *haptoglobin* are depressed in patients with parenchymal hepatic disease, both acute and chronic.[32]

FLOCCULATION TESTS (Fig. 7). Only several of the many flocculation tests that have been devised have been widely applied in this country. Each of these so-called stability tests depends on some depression of the albumin and alpha-1 globulin levels and perhaps a quali-

Table 7. *Relative Levels of Serum Proteins in Various Types of Jaundice*

TYPE AND CAUSE OF JAUNDICE	CHEMICAL FRACTIONATION		SPECIAL TESTS		ELECTROPHORETOGRAM				FUSION β-γ AREA
	ALBUMIN	GLOBULIN	MUCO-PROTEIN	HAPTO-GLOBIN	α^1	α^2	β	γ	
Prehepatic									
Retention	N	N	N	N	N	N	N	N	–
Production	N	N or ↑	↓	↓	↑ or N	↓	↓	↑ or N	–
Hepatic									
Hepatocellular									
Acute hepatitis	N or ↓	N or ↑	↓	↓	↑	N or ↓	N or ↑	↑ or N	–
Cirrhosis, Laennec's	↓	↑	↓	↓	↓	N	N or ↑	↑	+
Cirrhosis, postnecrotic, active	↓	↑ ↑ ↑	↓	↓	↓	↑	N or ↑	↑ ↑ ↑	–
Hepatocanalicular									
Acute cholestatic	N	N or ↑	N*	N*	N	↑ or N	↑	N or ↑	–
Primary biliary cirrhosis	↓	↑	N	N	↑	↑	↑ ↑	↑	–
Posthepatic									
Complete	↓ or N	N or ↑	↑ or N	↑ or N	↑	↑	↑ ↑	N or ↑	–
Incomplete	↓ or N	↑ or N	↑ or N	↑ or N	↑	↑ ↑	↑ ↑	↑	–

N = Normal
↓ or N = Usually decreased, occasionally normal.
N or ↓ = Usually normal, occasionally decreased.
N or ↑ = Usually normal, occasionally increased.
↑ or N = Usually increased, occasionally normal.

tative change in the albumin complex, some increase in the gamma globulin level and, for some, other changes in the plasma proteins.[44] Furthermore, the serum of patients with obstructive jaundice has the biologically convenient property of inhibiting some of these flocculation reactions.[2] Abnormal results with the thymol turbidity and cephalin flocculation reaction occur in approximately 90 per cent of patients with infectious hepatitis a somewhat smaller proportion of patients with serum hepatitis, and most patients with the hepatocellular form of drug hepatotoxicity.[44] The cephalin flocculation results are abnormal in about two thirds of the patients with cirrhosis, while the thymol values are abnormal in approximately one third of this group. Patients with posthepatic jaundice have a less than 10 per cent incidence of positive values for the cephalin flocculation tests. The incidence of slightly elevated thymol turbidity values is greater (25 per cent) in the incomplete obstruction of choledocholithiasis than in the complete obstruction of carcinoma of the pancreas (less than 10 per cent).[44]

There has been a recent tendency to regard the flocculation tests as less useful than the serum enzyme tests and too nonspecific to be of value in the differential diagnosis of jaundice. We regard them as useful adjuncts when the values are interpreted in the light of the other available data.

OTHER BIOCHEMICAL TESTS. Several other tests that have been introduced have met with little acceptance. These include measurement of serum levels of cyanocobalamine,[33] iron,[34] and bile acids.[7] Serum levels of *cyanocobalamine* and of *iron* are high in patients with acute hepatocellular jaundice as the result of release from damaged and necrotic liver cells. The values of these substances remain normal in most patients with chronic hepatic disease and in those with posthepatic or hepatocanalicular jaundice. Measurement of serum iron levels for dif-

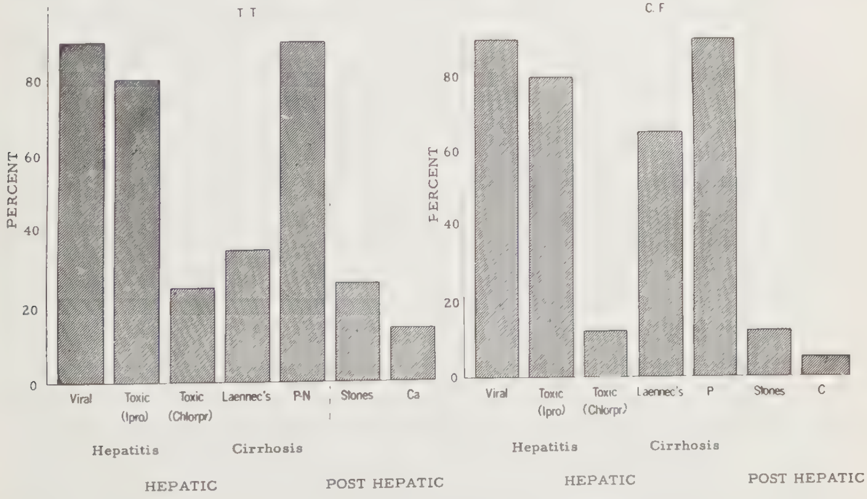

Figure 7. Incidence of abnormal values for thymol turbidity (T.T.) and cephalin flocculation (C.F.) tests in various entities that cause hepatic and posthepatic jaundice (from Zimmerman, H. J.[45]).

ferential diagnosis of jaundice is not widely practiced and that of cyancobalamine for this purpose is of only investigative interest.

Recent studies have demonstrated characteristic and distinctive abnormalities of the *serum bile acids* in hepatic and posthepatic jaundice.[7] In obstruction of the biliary tree, the total level of bile acids may be increased ten times or more, with a normal ratio of trihydroxy to dihydroxy bile acids. In patients with hepatitis, the increase in total bile acid level is less striking, and the ratio of tri to dihydroxy bile acids drops below the normal of 1.0. The technical feasibility and the clinical usefulness of this interesting phenomenon, however, remains to be proved.

SPECIAL PROCEDURES. The administration of corticosteroids leads to a rapid decrease in the bilirubin levels of patients with acute hepatitis, but to little change in those with posthepatic jaundice. Accordingly, a therapeutic trial with corticosteroids has been proposed to differentiate hepatic from posthepatic jaundice.[8, 38] Unfortunately, hepatocanalicular jaundice, the form of hepatic disease which simulates posthepatic jaundice most closely, shows relatively little effect, while the posthepatic jaundice which simulates hepatic disease most closely (obstruction due to stones or tumor in the common duct) can show a waning of jaundice coincident with the administration of steroids. In our opinion, this procedure offers little help in the differential diagnosis of jaundice.

The examination of *duodenal aspirate* for cholesterol crystals of bilirubin, though useful for the diagnosis of choledocholithiasis, has been abandoned in must laboratories. The technique of searching for neoplastic cells in the duodenal fluid, recommended some years ago[29] as an ancillary procedure for the diagnosis of carcinoma of the pancreas, has not been adopted widely.

Ordinary *radiographic* procedures may be of subsidiary assistance in the differential diagnosis of jaundice. Demonstration of gallstones, or the widened duodenal sweep infrequently produced by a pancreatic carcinoma and more commonly produced by a pseudocyst, may help establish the diagnosis. Compression of the duodenal bulb may be produced by a gallbladder carcinoma, and pancreatic lesions may produce a pressure defect in the second part of the duodenum.

Several techniques [27, 40] have been recommended for the application of ^{131}I-tagged *rose bengal* to the differential diagnosis of jaundice, but the clinical usefulness of any of them remains to be determined. Patients with hepatocellular jaundice are reputed to have a reduced uptake of tagged dye by the liver, but to excrete more into the duodenum than do patients with biliary obstruction. However, there appears to be considerable overlap between the groups. The usefulness of the recent refinement[40] of the technique that consists of determining the ratio of intestinal entry to hepatic uptake of dye remains to be established.

Measurement of radioactive triolein absorption has been reported[4] to be a promising procedure for the differential diagnosis of jaundice. Patients with posthepatic jaundice were found to have markedly impaired absorption, while patients with hepatocellular or hepatocanalicular jaundice appeared to have normal absorption of the labelled fat. The clinical value of this procedure remains to be demonstrated.

Percutaneous *transhepatic cholangiography*[26] can provide unequivocal evidence of posthepatic obstruction. Since there is some hazard of producing bile peritonitis by this procedure, its useful application as a diagnostic tool seems limited to the preoperative state. If it is performed immediately prior to exploratory laparatomy, no significant risk is added, the diagnosis can be confirmed, and the surgeon is helped by the demonstration of the site of obstruction.

Liver biopsy is of definite but limited value for the distinction of hepatic from posthepatic jaundice. While the respective histologic patterns of hepatocellular and posthepatic jaundice are usually clearly distinguishable, the procedure may offer some hazard of producing bile peritonitis in the patient with posthepatic jaundice. Furthermore, hepatocanalicular jaundice, which is the most difficult diagnosis to establish by clinical and biochemical criteria, may yield biopsy findings that also are inconclusive and may simulate those of posthepatic jaundice. Nevertheless, histologic differences between the two exist and, if identified, may help in the diagnosis. Neutrophilic infiltration of the portal areas and bile duct walls, staining of bile duct epithileum with bilirubin, and the presence of large bilirubin casts in the canaliculi and in the ducts of the portal areas point toward posthepatic jaundice. "Bile lakes" and "feathery necrosis" of the hepatocytes, when present, clearly identify the jaundice as posthepatic. In hepatocanalicular jaundice, portal inflammation is mononuclear and eosinophilic; bile casts are only in canaliculi, and there are no bile lakes. In defining the specific cause of hepatocellular jaundice, biopsy is usually diagnostic. For example, the acute hepatic necrosis of viral or toxic hepatitis is clearly distinguishable from the jaundiced phase of cirrhosis (steatonecrosis).

It is our practice to perform liver biopsy on patients whose jaundice we consider to be hepatic rather than posthepatic. If the weight of evidence points to posthepatic jaundice, however, transhepatic cholangiography followed by exploratory laparotomy seems preferable to biopsy.

Differential Diagnosis

A schematized representation of the differential diagnosis of jaundice exclusive of neonatal jaundice is illustrated in Figure 8. A ratio of direct to total bilirubin (D/T) of less than 0.2 with absence of bilirubin from the urine usually indicates prehepatic jaundice, while a high D/T ratio (greater than 0.4) with bilirubin in the urine indicates that the jaundice is hepatic or posthepatic. In a patient with prehepatic jaundice, elevated levels of urine and fecal urobilinogen, anemia with reticulocytosis or increased erythropoietic activity in the bone marrow, and decreased erythrocyte survival time indicate that the jaundice is production in type. Lack of reticulocytosis or anemia and normal values for urine and fecal urobilinogen indicate that the jaundice is of the retention type, probably Crigler-Najjar or Gilbert's syndrome. These two are easily distinguishable clinically, for the Crigler-Najjar syndrome produces deep jaundice and serious neurologic disease early in life, while Gilbert's disease is a benign condition that leaves health unimpaired and leads to only slightly or moderately elevated bilirubin levels (less than 8 mg. per 100 ml.).

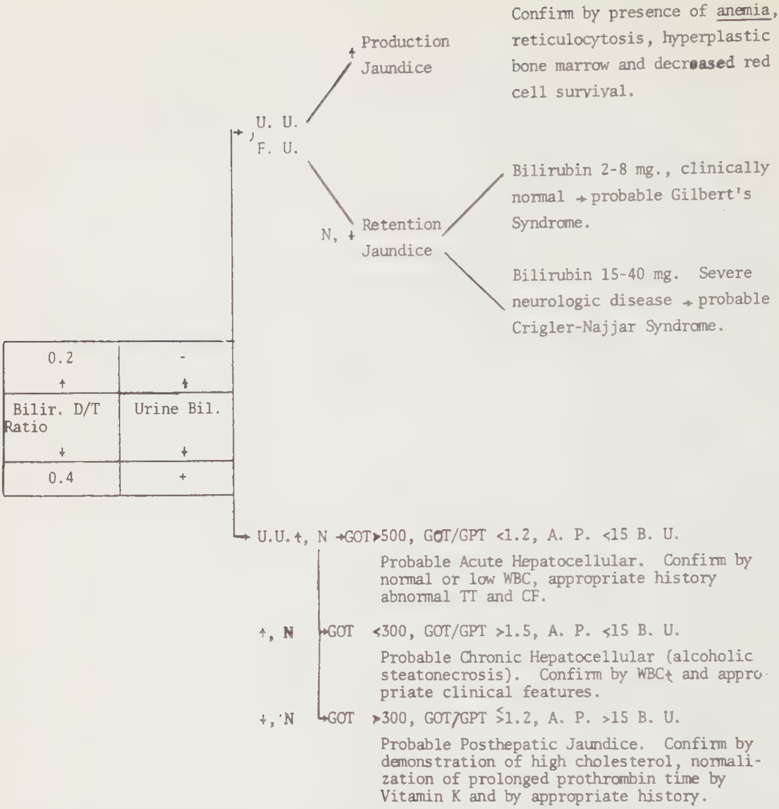
Production Jaundice
Confirm by presence of anemia, reticulocytosis, hyperplastic bone marrow and decreased red cell survival.
U. U.
F. U.
N, ↓
Retention Jaundice
Bilirubin 2-8 mg., clinically normal → probable Gilbert's Syndrome.
Bilirubin 15-40 mg. Severe neurologic disease → probable Crigler-Najjar Syndrome.
0.2
-
Bilir. D/T Ratio
Urine Bil.
0.4
+
U.U.↑, N →GOT>500, GOT/GPT <1.2, A. P. <15 B. U.
Probable Acute Hepatocellular. Confirm by normal or low WBC, appropriate history abnormal TT and CF.
↑, N →GOT <300, GOT/GPT >1.5, A. P. <15 B. U.
Probable Chronic Hepatocellular (alcoholic steatonecrosis). Confirm by WBC↑ and appropriate clinical features.
↓, N →GOT >300, GOT/GPT ≤1.2, A. P. >15 B. U.
Probable Posthepatic Jaundice. Confirm by demonstration of high cholesterol, normalization of prolonged prothrombin time by Vitamin K and by appropriate history.

Figure 8. Schematic view of approach to differential diagnosis of jaundice. "Bilir. D/T ratio" refers to ratio of conjugated serum bilirubin to the total serum bilirubin values. "Urine Bil." refers to urine bilirubin, "U.U." and "F.U." refers to urine and serum urobilinogen levels, respectively.

A D/T ratio greater than 0.4 and the demonstration of bilirubin in the urine indicates that the jaundice may be hepatic or posthepatic. When the urine levels of urobilinogen are also increased, it suggests but does not prove the diagnosis of hepatocellular jaundice. Evidence that the cause is acute viral or toxic hepatitis is provided by levels of GOT and GPT greater than 500 Karmen units, a relatively low GOT GPT ratio, an alkaline phosphatase value below 15 BU, lack of significant normalization of a prolonged prothrombin time after vitamin K administration, abnormal values for the flocculation tests, and a relatively normal electrophoretic pattern (save for mild elevation of gamma globulin level). A normal or low white blood cell count is typical of viral but not necessarily of toxic hepatitis. Similar values for the alkaline phosphatase level and the prothrombin time response to vitamin K are observed in chronic hepatocellular jaundice, but the values for GOT are much lower, the GOT/GPT ratio is relatively high, the values for the flocculation test are more erratic, the electrophoretogram shows low albumin and high gamma globulin levels, and the white blood cell count may be elevated (in alcoholic steatonecrosis).

Low urobilinogen levels in the urine (and feces if measured) suggest that the jaundice is posthepatic. Supporting evidence for this provided by an alkaline phosphatase level above 15 BU, a GOT value below 300 Karmen units, an approximately equal value for the GPT, normalization of a prolonged prothrombin time after vitamin K administration, normal values for the flocculation tests and an electrophoretic pattern that shows high alpha-2 and beta globulin levels.

Low urine urobilinogen values also may be a manifestation of hepatocanalicular jaundice, or even of the brief cholestatic phase of viral hepatitis. The cholestatic phase of viral hepatitis is recognized by its usual transience (1 or 2 weeks) and the demonstration of the parenchymal abnormalities of hepatocellular jaundice. Hepatocanalicular is difficult to distinguish from posthepatic jaundice. A history of exposure to drugs and associated clinical features of drug hypersensitivity may be of assistance in this regard. The few clues from the laboratory include slightly greater tendency to the hepatocellular type of abnormality in hepatocanalicular than in posthepatic jaundice. In doubtful cases, liver biopsy or a brief period of observation may be of help in establishing the diagnosis. Demonstration in biopsy specimens of eosinophils in the portal areas, and of small bile casts in the canaliculi, supports hepatocanalicular jaundice, while portal area neutrophilia, bile duct invasion by neutrophils, and large bile casts support the diagnosis of posthepatic jaundice. The period of observation rarely needs to exceed 2 weeks. The practice of waiting 6 weeks for jaundice to subside before a clear differential can be definitely made between "medical" and "surgical" jaundice is archaic. Generally, during a 2-week period of observation, doubtful values become clearly supportive of hepatic or posthepatic jaundice. Patients with jaundice that appears to be hepatic should not be explored surgically, irrespective of duration of the jaundice, but should be studied by biopsy; jaundice that appears to be posthepatic should lead to operation long before the 6-week period is over.

Despite these clear guidelines, some patients come to surgical exploration, because the differential diagnosis may be difficult. This is rarely necessary. In these patients, percutaneous transhepatic cholangiography, preoperatively, may help, and operative cholangiography is useful in defining the site of obstruction.

Almost all cases of jaundice can be separated into the hepatic and posthepatic categories. Identifying the specific cause is usually possible. Reappraisal of the clinical and laboratory features that have been enumerated facilitates the identification of hepatocellular jaundice as acute infectious, serum or toxic hepatitis, mononucleosis, or leptospirosis, or as cirrhosis (Table 8). The etiologic background, the acuteness of onset with or without preicteric fever, persistence of fever after jaundice has appeared, prominence of hepatomegaly or splenomegaly, presence of spider nevi, the extrahepatic manifestations, and the results of laboratory studies permit reasonably precise diagnosis.

Since the diagnosis of posthepatic jaundice is an indication for operation, distinction among the several causes may seem less urgent than the recognition that the jaundice is surgical. Nevertheless, fever, chills, abdominal pain, leukocytosis, and a past history of similar epi-

Table 8. *Features That Assist in Differential Diagnosis of Hepatocellular Jaundice*

	VIRAL HEPATITIS					CIRRHOSIS (ALCOHOLIC STEATONECROSIS)
	INFECTIOUS	SERUM	TOXIC	INFECTIOUS MONONUCLEOSIS	LEPTOSPIROSIS	
Onset: Acute	+	+	+	+	+	−
Onset: Prodromal fever	+	−	+	+	+	±
Fever with jaundice	−	−	±	+	+	+
Spider nevi	−	−	−	−	−	+
Hepatomegaly	±	±	±	±	±	4+
Splenomegaly	+	+	±	2+	±	2+
Lymph node enlargement	+	+	+	3+	−	−
Pneumonitis	−	−	−	±	+	−
Meningoencephalitis	−	−	−	±	3+	−
Leukocytosis	−	−	−	±	+	+
Differential WBC	L	L	Eos.	L	Neut.	Neut.
Abnormal lymphocytes	+	+	±	4+	−	−
Renal lesion	−	−	+	−	4+	±
Serologic diagnosis	−	−	−	+	+	−
Thymol turbidity test	4+	3+	3+	4+	2+	+
Cephalin flocculation test	4+	3+	3+	4+	2+	3+
GOT	4+	4+	2+	2+	+	+
GOT/GPT ratio	<1.2	<1.2	≧1.2	<1.2	?	>1.5

+ to 4+ = Degree of abnormality.
L = Relative lymphocytes.
Eos. = Eosinophils.
Neut. = Relative neutrophils.

sodes suggest strongly that the cause of the jaundice is choledocholithiasis (Table 9). An insidious, usually afebrile, weight-losing course, with chronic or no pain, points toward a diagnosis of carcinoma of the pancreas. Values for GOT above 300 Karmen units and for alkaline phosphatase below 15 Bodansky units and urobilinogenuria are more characteristic of gallstone obstruction than of obstruction due to pancreatic carcinoma. Common duct or ampullary tumors yield incomplete obstruction similar to that of choledocholithiasis, but with a more insidious onset and with less prominent fever, chills, and pain. The melena of ampullary carcinoma may be mimicked by that of common duct stones.

There are several sources of error in the differential diagnosis of jaundice (Table 10). Hepatic jaundice can simulate posthepatic, posthepatic jaundice can mimic hepatic, and there are instances of patients who have mixed types of jaundice.

Hepatic jaundice may simulate posthepatic under several sets of circumstances. The transient so-called obstructive phase of viral hepatitis, with high serum and urine bilirubin, low urine urobilinogen, and clay-colored stools, is usually easily recognized by a few days of observation and the evolution of a characteristic pattern including the degree and type of hypertransaminasemia and other evidence of parenchymal ab-

Table 9. *Differential Diagnosis of Posthepatic Jaundice*

FEATURES	HEPATO-CANALICULAR JAUNDICE	COMMON DUCT		PANCREATIC CA.
		STONES	CA.	
Onset	Acute	Acute	Chronic	Chronic
Fever	±	+	∓	–
Chills	±	+	∓	–
WBC ↑	± (Eos.)	+ (PMN)	± (PMN)	–
Pain	±	+	∓	∓
Previous episodes	–	+	∓	∓
Diabetes	–	–	–	+
Melena	–	∓	+	–
Alkaline phosphatase	>15 BU	≷15 BU	≷15 BU	>15 BU
Abnormal thymol turbidity test	25%	25%	<10%	<10%
Increased cephalin flocculation	10%	15%	5%	5%
GOT, GPT	<500 K.U.	<500 K.U.	<300 K.U.	<300 K.U.

normality. Also, there is relatively little difficulty in recognizing the 10 to 20 per cent of patients with infectious hepatitis in whom the GOT values are in a nondiagnostic range, provided sufficient attention is paid to the clinical circumstances. Similary, the 5 per cent of patients with viral hepatitis and high (greater than 15 BU) alkaline phosphatase values will not be misdiagnosed as having posthepatic jaundice if other biochemical measures and clinical features are carefully evaluated.

More perplexing is hepatocanalicular jaundice with a biochemical pattern indistinguishable from that of posthepatic jaundice. Acute onset, drug exposure, a febrile preicteric period, rash and eosinophilia, and subsidence after several weeks of observation are helpful in its recognition. Nevertheless, these are the patients who account for most of the small number of errors in the differential diagnosis of jaundice. It is essential to be aware of the large number of drugs that can produce the syndrome of hepatocanalicular jaundice that occurs in the third trimester of pregnancy, of primary biliary cirrhosis, and even of the familial types of jaundice that may present as posthepatic or atypical hepatic jaundice.

The vagaries of incomplete posthepatic jaundice must be well understood. The jaundice of one fourth of the patients with gallstone obstruction may simulate that of hepatic disease. The alkaline phosphatase may be below the "obstructive" range, the flocculation tests may be abnormal, the globulin level may be surprisingly high and the cholesterol level unexpectedly low for posthepatic jaundice, and the transaminase values may even be higher than the usual "obstructive" range. We have seen several patients with severe ascending cholangitis, secondary to gallstones, who have had GOT values above 500 units. Recognition of this syndrome depends on the clinical criteria of chills, fever, leukocytosis, and abrupt onset after pain. It should be recalled that about 10 per cent of patients with choledocholithiasis may deny typical or, indeed, any pain, and that clinical evidence of ascending cholangitis also may be absent.

There are a number of examples of jaundice of mixed pathogenesis

Table 10. *Pitfalls in Differential Diagnosis of Jaundice*

Hepatic jaundice that simulates posthepatic	Transient cholestatic phase of viral hepatitis Viral hepatitis with atypical values for biochemical tests Relatively slight evidence of parenchymal injury—values for GOT and GPT too low, or values for flocculation tests normal Relatively high alkaline phosphatase values Hepatocanalicular jaundice (pattern of biochemical abnormalities and clinical features that closely resemble those of posthepatic jaundice) Acute intrahepatic cholestasis (drug-induced or viral hepatitis or idiopathic) Jaundice of pregnancy Primary biliary cirrhosis Genetic syndromes (Dubin-Johnson or Rotor's, or benign recurrent familial cholestasis)
Posthepatic jaundice that simulates hepatic	Values of alkaline phosphatase and cholesterol atypically low, or of GOT, GPT and T.T., atypically high; particularly characteristic of stone or tumor of common duct
Jaundice of mixed pathogenesis	
Production + hepatocellular jaundice	Sickle cell disease Alcoholic with steatonecrosis and Zieve's syndrome Hodgkin's disease
Hepatocellular + posthepatic jaundice	Cirrhosis + choledocholithiasis Cirrhosis + pancreatitis
Hepatocellular + posthepatic + hemolytic	Alcoholic steatonecrosis + pancreatitis + Zieve's syndrome
Insufficient awareness of unusual syndromes	
Excessive reliance on clinical axioms or single tests	
Impatience to make a diagnosis after too short a period of observation	

(Table 10). Hepatocellular jaundice may complicate sickle cell anemia, and hemolysis may complicate cirrhosis or fatty liver. In Hodgkin's disease, there may be hemolytic jaundice, hepatocellular jaundice, or both. Incidentally, the posthepatic jaundice traditionally considered to result from lymphomatous nodes at the porta hepatis is a rare phenomenon.

The combinations of posthepatic and hepatic mechanisms of jaundice may be overlooked if not kept in mind. Patients with cirrhosis may have coincidental choledocholithiasis or the pancreatitis of alcoholism contributing to or responsible for the jaundice.

It is obvious that the lack of awareness of jaundice-producing syndromes can lead to misdiagnosis. Early patients with chlorpromazine jaundice or the Dubin-Johnson syndrome were subjected to surgical exploration, whereas recent instances have been identified by clinical, laboratory, and biopsy studies. It is worth recalling that some drugs produce hepatocellular jaundice that simulates viral hepatitis, others produce hepatocanalicular jaundice, and some produce mixed patterns.[11] Drug-induced hemolytic jaundice is, of course, well known.

Perhaps the most important pitfalls in diagnosis are the dependence on clinical axioms or on individual laboratory tests to distinguish all cases of jaundice, or the insistence on immediate diagnosis without the assistance of a brief period of observation.

REFERENCES

1. Arias, I. M.: Hepatic aspects of bilirubin metabolism. Ann. Rev. Med., *17*:257, 1966.
2. Arman-Cruz, R., Lobo-Parga, G., and Madrid, M.: The flocculation tests: A contribution to the study of their mechanism. J. Lab. Clin. Med., *39*:533, 1952.
3. Ballard, H., Bernstein, M., and Farrar, J. T.: Fatty liver presenting as obstructive jaundice. Amer. J. Med., *30*:196, 1961.
4. Berkowitz, D., Shlaroff, D. M., and Tumen, H. J.: The use of radioactive tagged lipids in the differential diagnosis of jaundice. Gastroenterology, *40*:513, 1961.
5. Billing, B. H.: The disposal of bilirubin. *In* Popper, H., and Schaffner, F.: Progress in Liver Diseases. New York, Grune and Stratton, 1964, Vol. II, pp. 1-14.
6. Billing, B. H., Williams, R., and Richards, T. G.: Defects in hepatic transport of bilirubin in congenital hyperbilirubinemia: An analysis of plasma bilirubin disappearance curves. Clin. Sci., 27.245, 1964.
7. Carey, J. B., Jr.: The serum trihydroxy-dihydroxy bile acid ratio in liver and biliary tract disease. J. Clin. Invest., *37*:1494, 1958.
8. Chalmers, T. C., Gill, R. J., Jernigan, T. P., Svec, F. A., Jordan, R. S., Waldstein, S. S., and Knowlton, M.: Evaluation of 4-day ACTH test in differential diagnosis of jaundice. Gastroenterology, *30*:894, 1956.
9. Crigler, J. F., Jr., and Najjar, V. A.: Congenital familial non-hemolytic jaundice with kernicterus. Pediatrics, *10*:169, 1952.
10. Deutsch, E.: Blood coagulation studies in liver disease. *In* Popper, H., and Schaffner, F.: Progress in Liver Diseases. New York, Grune and Stratton, 1964, Vol. II, pp. 69-83.
11. Dubin, I. N., and Johnson, F. B.: Chronic idiopathic jaundice with unidentified pigment in liver cells: New clinicopathologic entity with report of 12 cases. Medicine, *13*:155, 1954.
12. Dubin, I. N., Sullivan, B. H., Jr., Le Golvan, D. C., and Murphy, L. C.: The cholestatic form of viral hepatitis: Experiences at Brooke Army Hospital during the years 1951 to 1953. Amer. J. Med., 29:55, 1960.
13. Ducci, H.: Contribution of the laboratory to the differential diagnosis of jaundice. J.A.M.A., *135*:695, 1947.
14. Greene, C. H.: Differential diagnosis of jaundice. J.A.M.A., *171*:1780, 1959.
15. Gregory, C. H., and Watson, C. J.: Studies of conjugated bilirubin. II. Problems of sulfates of bilirubin *in vivo* and *in vitro*. J. Lab. Clin. Med., *60*:17, 1962.
16. Hamilton, J. R., and Sass-Kortsak, A.: Jaundice associated with severe bacterial infection in young infants. Pediatrics, *63*:121-132, 1963.
17. Harinasuta, U., Chomet, B., Ishak, K., and Zimmerman, H. J.: Steatonecrosis – Mallory body type. Medicine, *46*:2, 1967.
18. Haubrich, W. S.: Adverse hepatic reactions to halothane: Risks and safeguards. Chicago Med. Sch. Quart., *26*:95, 1966.
19. Hobbs, J. R.: Serum proteins in liver disease. Proc. Roy. Soc. Med., *60*:1250, 1967.
20. Holtzman, I. N.: Sarcoidosis followed by biliary cirrhosis and xanthomatosis. N.Y. State J. Med. "Case Reports," *61*, 1961.
21. Holzbach, R. T., and Sanders, J. H.: Recurrent intrahepatic cholestasis of pregnancy: Observations on pathogenesis. J.A.M.A., *193*:542, 1965.
22. Huete-Armijo, A., and Exton-Smith, A. N.: Causes and diagnosis of jaundice in elderly. Brit. Med. J., *4*:1113, 1962.
23. Iber, F.: Cholestasis. Postgrad. Med., *30*: 1967.
24. Israels, L. G., Suderman, H. J., and Ritzman, S. E.: Hyperbilirubinemia due to an alternate path of bilirubin production. Amer. J. Med., 27:693, 1959.
25. Kantrowitz, P. A., Jones, W. A., Greenberger, N. J., and Isselbacher, K. J.: Severe postoperative hyperbilirubinemia simulating obstructive jaundice. New Eng. J. Med., *276*:591-598, 1967.
26. Kaplan, A. A., Traitz, J. J., Mitchel, S. D., and Block, A. L.: Percutaneous transhepatic cholangiography. Ann. Int. Med., *54*:856, 1961.

27. Kawaguchi, J., Berk, E., and Soble, A. R.: Studies with I^{131}-labelled rose bengal. II. Clinical evaluation of a modified technique for differential diagnosis of jaundice. Amer. J. Digest. Dis., 7:300, 1962.
28. Klatskin, G.: Bile pigment metabolism. Ann. Rev. Med., *12*:211, 1961.
29. Lemon, H. M., and Byrnes, W. W.: Cancer of the biliary tract and pancreas. J.A.M.A., *141*:254, 1949.
30. Lester, R., Schumer, W., and Schmid, R.: Intestinal absorption of bile pigments. IV. Urobilinogen absorption in man. New Eng. J. Med., 272:939-943, 1965.
31. Mandema, E., deFraiture, W. H., Nieweg, H. O., and Arends, A.: Familial chronic idiopathic jaundice (Dubin-Sprinz disease) with a note on bromsulphalein metabolism in this disease. Amer. J. Med., *28*:42, 1960.
32. Owen, J. A., Padanyi, R., and Smith, H.: Serum haptoglobins and other tests in the diagnosis of hepatobiliary disease. Clin. Sci., *21*:189, 1961.
33. Rachmielewitz, M., Aronovitch, J., and Grossowicz, W.: Serum concentration of vitamin B_{12} in acute and chronic liver disease. J. Lab. Clin. Med., *48*:339, 1956.
34. Schamroth, L., Edelstein, W., Politzer, W. M., and Stevens, W.: Serum iron in the differential diagnosis of hepatobiliary disease. Brit. Med. J., *1*:960, 1956.
35. Schmid, R.: Hyperbilirubinemia. *In* Stanbury, J. B., Wyngaarden, J. B., and Frederickson, D. S., eds.: The Metabolic Basis of Inherited Disease. 2nd ed. New York, McGraw-Hill Book Co., 1966, pp. 871-902.
36. Sherlock, S.: Biliary secretory failure in man: The problem of cholestasis. Ann. Int. Med., *65*:397, 1966.
37. Somerskill, W. H. J.: The syndrome of benign recurrent cholestasis. Amer. J. Med., *38*:298, 1965.
38. Somerskill, W. H. J., and Jones, F. A.: Corticotrophin and steroids in the diagnosis and management of "obstructive jaundice." Brit. Med. J., 2:1499, 1958.
39. Stauffer, M. H., Sauer, W. G., Dearing, W. H., and Baggenstoss, A. H.: The spectrum of cholestatic hepatic disease. J.A.M.A., *191*:829, 1965.
40. Taplin, G. V., Meredith, O. M., Jr., and Kade, H.: Development of a radioisotope tracer for the differential diagnosis of jaundice (the rose bengal-I^{131} hepatogram). J. Louisiana M. Soc., *109*:255, 1957.
41. Thorling, L.: Jaundice in pregnancy: A clinical study. Acta. Med. Scand., Suppl. 302, 1955.
42. Weinstein, B. R., Korn, R. J., and Zimmerman, H. J.: Obstructive jaundice as complication of pancreatitis. Ann. Int. Med., *58*:245, 1963.
43. Zieve, L.: Jaundice, hyperlipemia and hemolytic anemia: A heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. Ann. Int. Med., *48*:471, 1958.
44. Zimmerman, H. J.: Clinical and laboratory manifestations of hepatotoxicity. Ann. N.Y. Acad. Sci., *104*:954, 1963.
45. Zimmerman, H. J.: Liver function tests. Modern Treatment, *1*:490, 1964.
46. Zimmerman, H. J.: Serum enzymes in the diagnosis of hepatic disease. Gastroenterology, *46*:613, 1964.

Veterans Administration Hospital
150 South Huntington Avenue
Boston, Massachusetts 02130

Cirrhosis in Alcoholics

CARROLL M. LEEVY, M.D.*

Morbidity and mortality from cirrhosis in alcoholics has continued to increase during the past decade despite major advances in our knowledge of its pathogenesis and natural history. This is attributable to the increased incidence of alcoholism and failure to appropriately utilize available preventive and therapeutic measures.[10] The occurrence of cirrhosis in alcoholics varies depending upon the amount, frequency, and type of alcoholic beverage ingested; dietary habits; and presence of other causes of hepatic injury. This condition is not progressive, and prognosis is good if alcohol intake is stopped before the development of evidence of liver failure.[14] In contrast, once an alcoholic with cirrhosis develops ascites, bleeding esophageal varices, mental changes, or renal dysfunction, life expectancy is reduced and may not be altered by currently available symptomatic measures.[1, 6, 26] A three-phase program which detects early phases of cirrhosis, provides treatment of acute symptoms due to hepatic and nutritional abnormalities, and initiates long-term medical and psychiatric care can significantly reduce morbidity and mortality resulting from alcoholism.[14, 16] Wide adoption of this or a similar model is needed. This paper reviews medical considerations upon which such programs should be based and extended.

DEFINITION AND PATHOPHYSIOLOGY

Cirrhosis in alcoholics is characterized by a finely nodular or grossly deformed liver which may be smaller or larger than normal. The gross appearance of the liver results from diffuse or localized fibrosis and nodular regeneration of liver cells, which distort the hepatic lobule and alter its vascular, lymphatic, and biliary networks. Microscopic study reveals varying amounts of fat, liver cell necrosis, inflammation, mesenchymal cell replication, and bile duct proliferation. Functional capacity

---

From the Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine, the East Orange Veterans Administration Hospital, and Newark City Hospital

*Chief of the Medical Service, Veterans Administration Hospital, East Orange, New Jersey; Professor and Director, Division of Hepatic Metabolism and Nutrition, New Jersey College of Medicine, Jersey City, New Jersey

Supported by NIH grant AM-04437, and a grant from the New Jersey State Department of Health, Division of Chronic Illness Control

Medical Clinics of North America—Vol. 52, No. 6, November, 1968

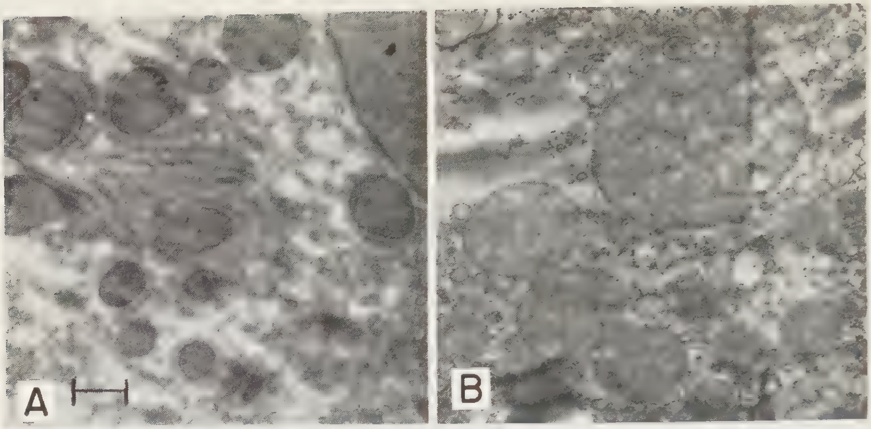

Figure 1. Electron micrograph of liver biopsy specimen from a human volunteer, showing normal mitochondria and endoplasmic reticulum (*A*) and enlarged mitochondria and vesiculation of the endoplasmic reticulum after receipt of 1 pint of ethanol daily for 3 weeks (*B*).

depends upon the severity and activity of the cirrhotic process; it is regularly reduced in severe cirrhosis. In contrast, alcoholics with mild to moderate cirrhosis usually exhibit reversible signs and symptoms of liver failure during active phases of the disease, and may have no significant impairment of liver function with inactivity of the pathologic process.[11]

Cirrhosis develops when alcoholic beverages are ingested in sufficient quantity to interfere with normal dietary patterns for long periods of time. Ethanol, in the setting of nutritional deficiency, is responsible for this condition;[10] however, viral hepatitis and other causes of liver injury may contribute to its development. Morphologic events leading to cirrhosis have now been delineated by serial biopsies in volunteers fed ethanol on a controlled basis. There is usually vesiculation of the endoplasmic reticulum, mitochondrial swelling, and accumulation of neutral fat (Fig. 1) in patients fed 1 pint of ethanol for 3 to 4 weeks, with or without an adequate diet.[28]

Long-term studies in two patients in our clinic indicate that if a pint of ethanol is continued while the patient receives a nutritious diet with vitamin supplements, morphology returns to normal within 2 to 3 months. Moreover, addition of ethanol to a high-protein diet in no way interferes with mobilization of liver fat or improvement of cirrhosis.[5, 27] On the other hand, serial liver biopsies revealed the appearance of liver cell necrosis, inflammation, mesenchymal cell proliferation, and early fibrosis in three patients maintained on a low-protein diet and given progressively larger doses of ethanol for 1 to 2 months.[8] Studies of in vitro nucleic acid synthesis show that proliferation of mesenchymal cells, in response to liver cell damage (Fig. 2), is a key reaction in the development of fibrosis and distortion of the hepatic lobule.[9] Long-term observations indicate that if alcoholism continues, patients with

Laennec's cirrhosis will develop postnecrotic features, and hepatoma will occur in one third of those with severe cirrhosis[17] (Fig. 3). It is convenient for discussion purposes to define four distinct developmental phases of alcoholic cirrhosis: first, fatty liver with minor subcellular changes; second, hepatitis with active necrosis and inflammation; third, fibrosis, ductular proliferation, and nodular regeneration leading to lobular distortion; and fourth, lobular distortion with postnecrotic features or hepatoma.

Biliary tract changes, liver cell dysfunction, and circulatory alterations which may occur in any of these developmental phases are responsible for manifestations of liver failure: (a) hyperbilirubinemia occurs because of increased production, decreased uptake, reduced conjugation, or reduced excretion of bilirubin;[18] (b) portal hypertension and its sequelae result from hyperplasia of sinusoidal cells,[21] distortion of the hepatic lobule, or opening of arteriovenous shunts;[24] (c) ascites occurs because of obstruction of hepatic venous and lymph outflow, hypoalbuminemia, and secondary hyperaldosteronism;[7] (d) mental changes are attributable to reduced cellular oxidative metabolism; insufficiency or unavailability of coenzyme A and acetyl A appears to be a key defect in this state;[30] (e) renal failure may occur in kidneys which function normally when transplanted into subjects without hepatic insufficiency, and is characterized by a decrease in renal blood flow and increased renal vascular resistance.[1]

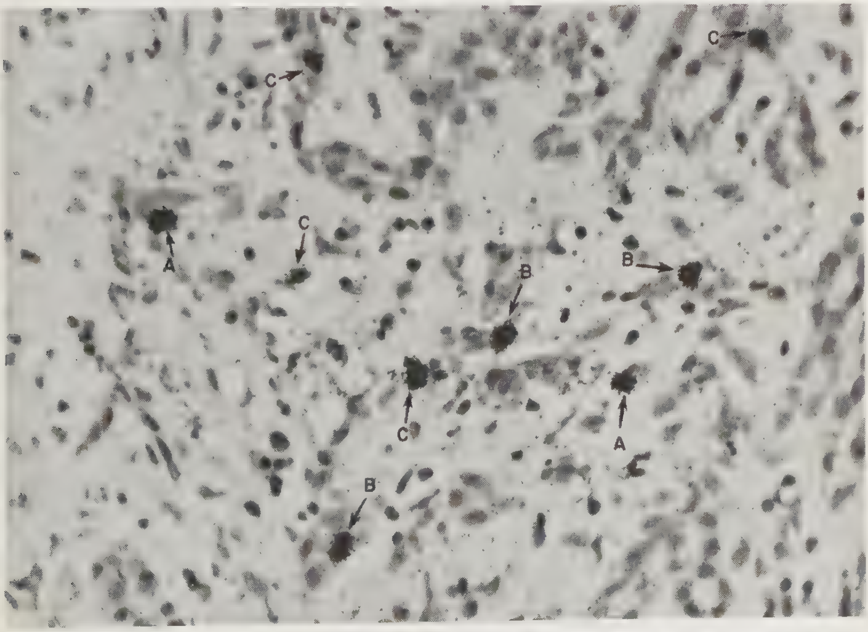

Figure 2. Autoradiograph following incubation of human biopsy specimen in tritiated thymidine which demonstrates regenerative response to ethanol-induced liver cell necrosis: *A*, parenchymal cells; *B*, ductular cells; and *C*, mesenchymal cells.

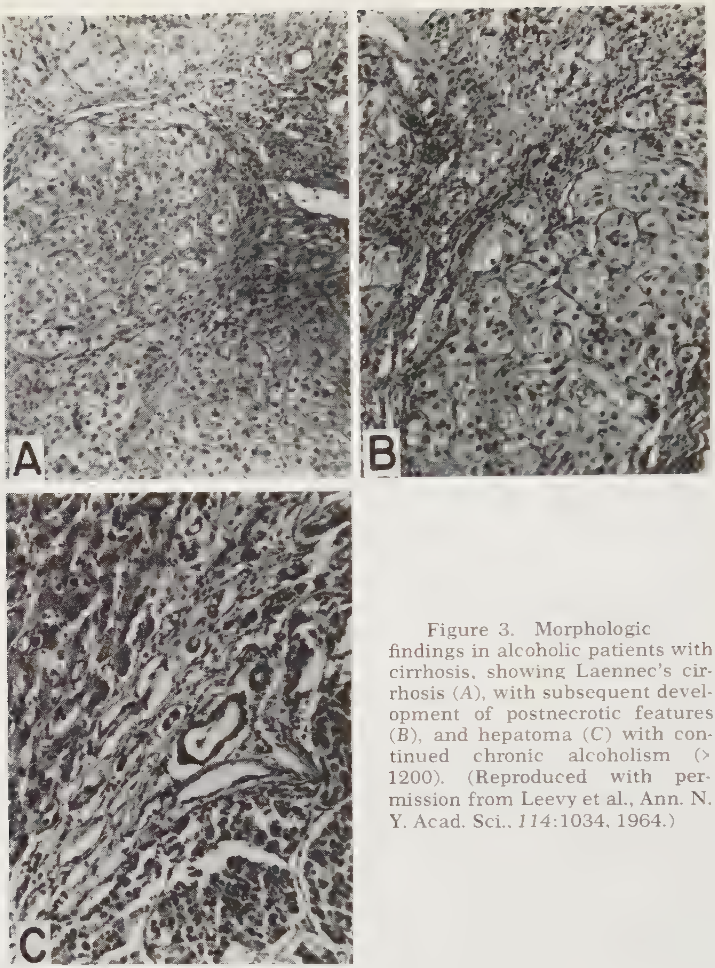

Figure 3. Morphologic findings in alcoholic patients with cirrhosis, showing Laennec's cirrhosis (*A*), with subsequent development of postnecrotic features (*B*), and hepatoma (*C*) with continued chronic alcoholism (× 1200). (Reproduced with permission from Leevy et al., Ann. N. Y. Acad. Sci., *114*:1034, 1964.)

INCIDENCE AND SUSCEPTIBILITY

Histologic evidence of cirrhosis was present in 30 per cent of 3000 hospitalized patients in whom there was a history of chronic alcoholism which interfered with work and social responsibilities.[10] The incidence was approximately the same in alcoholics with delirium tremens and those admitted for other illnesses. Normal liver morphology was present in an equal number of patients with chronic alcoholism and was attributed to (a) inherent capacity to repair liver damage despite continued alcoholism; (b) constitutional or genetic resistance to liver injury; and (c) periodic interruption of alcohol intake. Ethanol, in sufficient quantity and frequency, regularly causes liver cell damage; however, there is a natural tendency to repair morphologic abnormalities. Seven patients (one under controlled conditions on a research ward) exhibited normal liver morphology although they had ingested 1 to 2 pints of ethanol daily for 6 to 8 months. Equally important is the development of acute intercurrent illness which necessitates discontinuation of alcohol. Two thirds of 45 confirmed alcoholics, studied over a 10-year period, periodically stopped alcohol ingestion because of behavior problems or gastrointestinal disturbances.

Role of Ethanol

Ethanol-induced fat deposition and liver cell damage has been attributed to the effect of NADH accumulation resulting from alcohol oxidation. Intravenous administration of 1.5 to 2.0 gm. of ethanol per kg. over a 1-hour period causes a significant increase in this cofactor in normal human volunteers. The NADH begins to return to pretreatment levels 8 hours later. An elevation of NADH persists for a longer period in patients with evidence of mitochondrial damage or fragmentation of the endoplasmic reticulum; however, there is no evidence to indicate that this either produces morphologic damage or increases ethanol toxicity.[20]

Ability to oxidize ethanol is of major importance in determining susceptibility to hepatic injury. Ethanol oxidative capacity is dependent upon activity of hepatic alcohol dehydrogenase and the levels of phosphopyridine nucleotides. It has been found that in addition to alcohol dehydrogenase in the cell sap, which is NAD-dependent,[2] there is a dehydrogenase or oxidase in the microsomal fraction of liver cells, which is NADP-dependent.[28] Liver cell damage decreases alcohol dehydrogenase activity, so that large amounts of ethanol, in itself, initially reduce tolerance; subsequently, alcohol tolerance may return to normal or become supernormal with repair of liver injury or proliferation of smooth endoplasmic reticulum. Patients with cirrhosis, unlike the person with normal liver or reversible liver damage, usually exhibit persistently low hepatic alcohol dehydrogenase activity and, therefore, have increased susceptibility to further liver cell damage (Fig. 4).

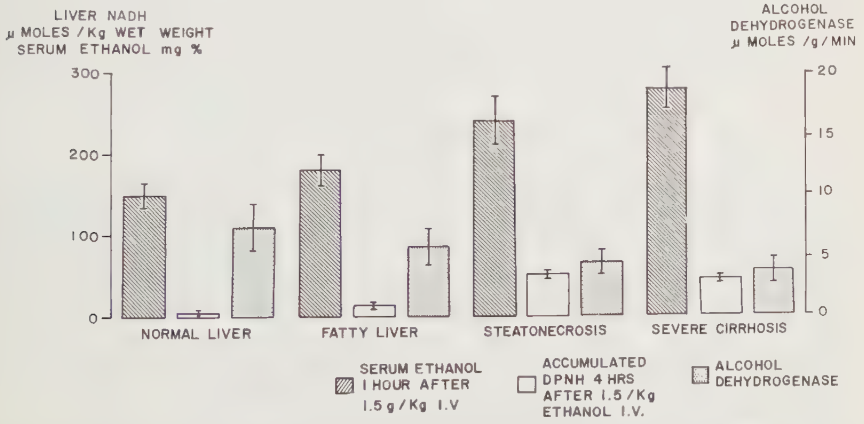

Figure 4. Influence of liver injury on hepatic activity of alcohol dehydrogenase, NADH accumulation and ethanol tolerance. (Reproduced with permission from Leevy, Fed. Proc., 26:1474, 1967.)

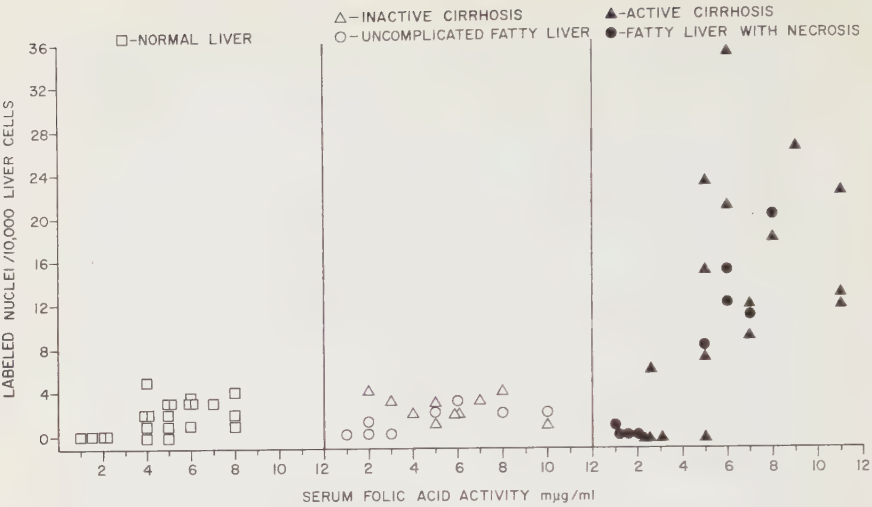

Figure 5. Relationship of in vitro DNA synthesis and serum folate levels in liver disease in the alcoholic.

Food

Chronic hepatic injury in the alcoholic is favored by dietary deficiency and prevented by a high-protein diet[25] or administration of androgenic-anabolic steroids.[8] Anabolic steroids may be effective by inducing hyperplasia of the endoplasmic reticulum, increasing synthesis of RNA, or facilitating incorporation of amino acids into protein. Liver destruction, which results from ingestion of alcoholic beverages, increases the need for nutrients required for cell repair or replication.[10] Minimal requirements for protein, vitamins, and minerals are increased. This is illustrated by studies of folic acid, the most often deficient vitamin in alcoholics. Nucleic acid synthesis is interfered with unless supplemental folic acid is provided in patients with ethanol-induced hepatic damage (Fig. 5). This prevents liver regeneration and may interfere with an adaptive increase of alcohol dehydrogenase activity.[10]

RECOGNITION

Alcoholic liver disease should be recognized during its inception. This is possible only by liver biopsy, which permits differentiation of normal liver, fatty liver, and alcoholic hepatitis from cirrhosis, and establishment of the activity and severity of these lesions. Serial biopsies, with in vitro nucleic acid synthesis, are desirable to evaluate the influence of therapy on the reparative process. Intrahepatic pulp pressure measurements should be obtained at the time of liver biopsy to determine if portal hypertension, which is responsible for many of the complications of cirrhosis, is present (Fig. 6).

Available biochemical liver function tests, except for dye excretion studies, are of little value. The cephalin-cholesterol flocculation and

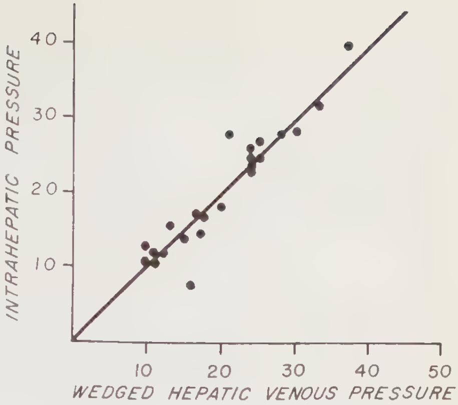

Figure 6. Correlation of intrahepatic pulp pressure and wedged hepatic vein pressure in liver disease.

thymol turbidity tests are nonspecific; serum transaminases are often normal because of protein or vitamin B_6 depletion, which interferes with hepatic production and release of enzymes.[23] Sulfobromophthalein (BSP) is widely used to detect liver injury in the alcoholic; however, its extrahepatic removal and the need to obtain repeated blood samples to calculate clearance accurately makes it less useful than indocyanine green (ICG), which is entirely removed from the circulation by the liver and can be evaluated by dichromatic ear densitometry.[19] Detection of early phases of liver disease in alcoholics is possible by use of 5.0 mg. per kg. of ICG; serial study of liver function in alcoholic patients with cirrhosis is best achieved by a dose of 0.5 to 2.5 mg. per kg. of this dye (Fig. 7).

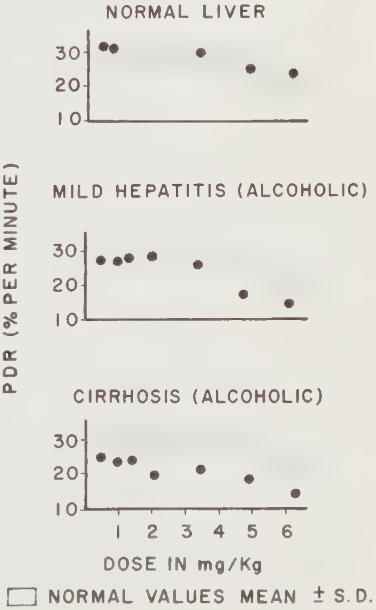

Figure 7. Removal rate of indocyanine green using various doses of dye in liver disease in the alcoholic. (Reproduced with permission from Leevy et al., J.A.M.A., *200*:236, 1967.)

Alcoholic patients with cirrhosis frquently exhibit evidence of a specific deficiency of a vitamin or mineral, neurologic disease, gastritis, pancreatitis, or cardiac abnormalities which require special clinical and laboratory studies. A chest x-ray, serologic study for syphilis, and urinalysis are indicated because of the high incidence of pulmonary tuberculosis, venereal disease, and pyelonephritis. Special studies are necessary to determine if esophageal varices (barium studies, esophagoscopy, or splenoportography), or subclinical mental changes (design construction, electroencephalograph study, blood ammonia) are present.

THERAPEUTIC ASPECTS

Abstinence from alcoholic beverages and ingestion of a nutritious diet are cornerstones of the treatment of cirrhosis of the alcoholic. Control of alcohol is only possible if the physician caring for the alcoholic has a sympathetic attitude with genuine clinical interest in both social and medical problems. A carefully planned, individual program of long-term care should be initiated during the first contact. The existence of cirrhosis, the necessity for complete abstinence, and the consequences for liver function of continued imbibing must be explained during a series of interviews. After control of acute signs and symptoms, the status of the hepatic process should be re-evaluated by physical examination, dye clearance, and biopsy at appropriate intervals. Tranquilizing drugs and supportive psychotherapy, such as can be provided by a physician, or through mutual support of Alcoholics Anonymous, are invaluable aids.[16]

Vitamin depletion, magnesium deficiency, hypoproteinemia, and electrolyte imbalance are common. Over 40 per cent of malnourished alcoholics with cirrhosis had hypovitaminosis with a significant decrease in circulating levels of two or more B-complex vitamins.[13] Prolonged ingestion of a nutritious vitamin-supplemented diet is necessary to correct these deficiencies and supply extra nutrients needed to repair damaged liver cells. There is occasional refractoriness to dietary therapy because of a malabsorption syndrome. Absorption of certain nutrients may be diminished because of intestinal or hepatic changes. Thus, a marked reduction in intestinal absorption of ^{35}S-thiamine has been noted in malnourished alcoholics with fatty liver or cirrhosis, and returns to normal only after prolonged nutritional therapy.[29]

It is necessary to avoid aggravation of liver damage by trauma, infections, and hepatotoxic drugs. Cognizance of the influence of drugs used in treatment of intercurrent diseases on hepatic morphology and function is necessary.[11] Severe liver injury prolongs the half-life of drugs which are oxidized, conjugated, stored, or excreted by the liver; however, hepatic dysfunction may also alter normal removal of drugs primarily excreted by the kidney. Thus chlordiazepoxide (Librium), a drug which is converted into a lactan by the liver, but whose removal primarily occurs via the kidney, exhibits a significant prolongation of half-life in patients with severe cirrhosis (Fig. 8).

Supportive therapy is necessary in decompensated cirrhosis. Portal hypertension, which contributes importantly to ascites, bleeding esophageal varices, or mental changes, may respond to a medical regimen in alcoholics with mild to moderate cirrhosis.[15, 22] A variety of surgical procedures have been proposed for treatment of an elevated portal pressure and relief of symptoms of liver failure refractory to medical therapy. None of these, with the possible exception of transplant of a liver or its lobe, can improve over-all hepatic function. Particular care must, therefore, be used in selecting an alcoholic with cirrhosis for such surgery.

A specific schema is necessary for medical treatment of each of the complications of cirrhosis because of the variety of available therapeutic approaches. It is important to document responsiveness: daily body weight and urinary sodium excretion, in ascites;[12] frequent hematocrit and observations for blood loss with bleeding esophageal varices; and blood ammonia and evaluation of mentation in hepatic coma. In addition to the specific measures described in accompanying articles, it is essential to identify any nutrient deficiency which may be responsible for aregenerative phases of liver injury. Malutilization of critical nutrients may be a limiting factor which cannot be overcome in the malnourished alcoholic by current therapeutic approaches. Thus a study of thiamine metabolism reveals that patients with cirrhosis often have a defect in phosphorylation or apoenzyme synthesis. This leads to deficient production of transketolase and pyruvate decarboxylase, clinically reflected in reduced red blood cell transketolase, hyperpyruvatemia, and persistent neurological abnormalities. Such patients occasionally fail to utilize thiamine because of defective nucleic acid synthesis. Three alcoholic patients with Wernicke's encephalopathy and reduced hepatic DNA and RNA synthesis due to folate and B_{12} deficiency exhibited refractoriness to thiamine therapy until nucleic acid metabolism returned to normal.[3]

Synthetic androgenic-anabolic steroids offer a promising new thera-

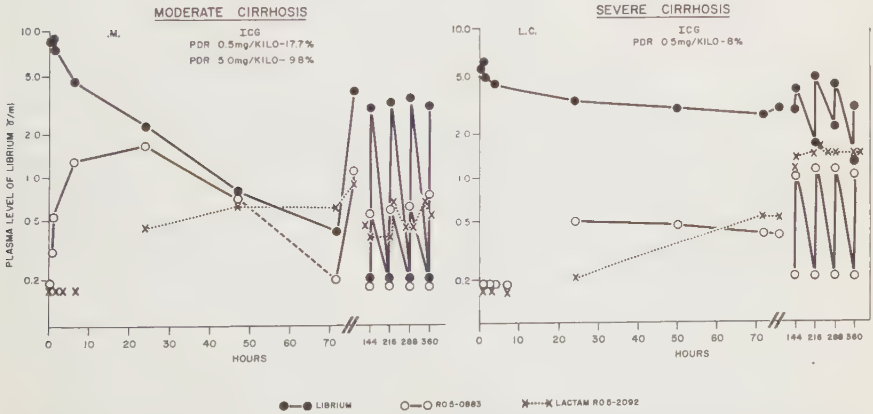

Figure 8. Disappearance rate of librium in an alcoholic with moderate cirrhosis who exhibits normal clearance as compared with an alcoholic with severe cirrhosis and decreased clearance.

peutic approach for interrupting progressive liver failure in selected patients with cirrhosis refractory to dietary therapy. These agents stimulate hepatic RNA synthesis, facilitate incorporation of amino acids into protein, and cause proliferation of smooth endoplasmic reticulum. Potential toxicity has greatly limited their use clinically, although they are of value in mobilization of liver fat and temporary correction of hypoprothrombinemia in some patients with liver failure. Attempts are underway to modify chemical structure of anabolic steroids so as to provide anabolism without untoward effects; availability of such agents would significantly reduce morbidity and mortality from alcoholic cirrhosis.

SUMMARY AND CONCLUSIONS

Cirrhosis occurs in approximately 30 per cent of subjects when consumption of alcoholic beverages is sufficient to interfere with work and social responsibilities. Experimental observations in human volunteers indicate that it develops in the setting of nutritional deficiency and liver cell damage induced by ethanol. In vitro studies of hepatic DNA synthesis in these subjects show the regenerative response evoked by liver cell necrosis to be responsible for fibrosis and lobular distortion, characteristic of cirrhosis. The incidence of cirrhosis in alcoholics is diminished by factors which interrupt ethanol intake or improve nutritional status, and is increased by superimposition of other causes of liver injury.

Liver biopsy and dye clearance studies should be obtained routinely in alcoholics to detect hepatic abnormalities prior to development of cirrhosis. Prophylaxis and treatment of cirrhosis in the alcoholic consist of abstinence from ethanol and provision of a nutritious vitamin-supplemented diet. Special measures may be necessary because of defective absorption or malutilization of essential nutrients. Therapy should be modified in patients with evidence of liver failure and an effort made to avoid drugs which increase hepatic dysfunction.

REFERENCES

1. Baldus, W. P., Feichter, R. N., Summerskill, W. H. J., Hunt, J. C., and Wakim, K. G.: The kidney in cirrhosis. II. Disorders of renal function. Ann. Int. Med., *60*:366, 1964.
2. Cherrick, G. R., and Leevy, C. M.: The effect of ethanol metabolism on levels of oxidized and reduced nicotinamide adenine dinucleotide in liver, kidney and heart. Biochem. Biophys. Acta, *107*:29, 1965.
3. Cole, M., Turner, A., Frank, O., Baker, H., and Leevy, C. M.: Observations on thiamine metabolism in Wernicke's encephalopathy. Amer. J. Clin. Nutr., *18*:303, 1966.
4. Conn, H. O., and Lindenmuth, W. W.: Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. A preliminary report of a controlled study. New Eng. J. Med., *266*:743, 1962.
5. Erenoglu, E. E., Edreira, J. G., and Patek, A. J., Jr.: Observations on patients with Laennec's cirrhosis receiving alcohol while on controlled diets. Ann. Int. Med., *60*:814, 1964.
6. Garceau, A. J., Donaldson, R. M., O'Hara, E. T., Callow, A. D., Muench, H., and Chalmers, T. C.: A controlled trial of prophylactic portacaval-shunt surgery. New Eng. J. Med., *270*:496, 1964.
7. Hanger, F. M.: Pathogenesis and management of ascites. Transcription of a panel meeting. Bull. N.Y. Acad. Med., *39*:238, 1963.
8. Jabbari, M., and Leevy, C. M.: Protein anabolism and fatty liver of the alcoholic. Medicine, *46*:131, 1967.

9. Leevy, C. M.: Abnormalities of hepatic DNA synthesis in man. Medicine, *45*:423, 1966.
10. Leevy, C. M.: Clinical diagnosis, evaluation and treatment of liver disease in alcoholics. Fed. Proc., *26*:1474, 1967.
11. Leevy, C. M.: Evaluation of Liver Function in Clinical Practice. Indianapolis, Lilly Research Laboratories, 1965.
12. Leevy, C. M.: Fluid and electrolyte metabolism in liver disease. *In* Sunderman, F. W., and Sunderman, F. W., Jr., eds.: Clinical Pathology of the Serum Electrolytes. Springfield, Ill., Charles C Thomas, 1966, p. 353.
13. Leevy, C. M., Baker, H., tenHove, W., Frank, O., and Cherrick, G. R.: B-complex vitamins in liver disease of the alcoholic. Amer. J. Clin. Nutr., *16*:339, 1965.
14. Leevy, C. M., Cunniff, C. L., Walton, D., and Healey, M.: Organization and function of a clinic for the alcoholic patients with liver disease. Quart. J. Stud. Alcohol, *15*:537, 1954.
15. Leevy, C. M., and Davidson, E.: Portal hypertension and hepatic coma. Postgrad. Med., *41*:84, 1967.
16. Leevy, C. M., Davidson, E., and Jeghers, H.: Acute alcoholism in the general hospital. Hospital Medicine, 2:24, 1965.
17. Leevy, C. M., Gellene, R., and Ning, M.: Primary liver cancer in cirrhosis of the alcoholic. Ann. N.Y. Acad. Sci., *114*:1026, 1964.
18. Leevy, C. M., and Paumgartner, G.: Jaundice and alcoholism. Proc. Internatl. Symposium on Jaundice, Freiburg, Germany, in press.
19. Leevy, C. M., Smith, F., Longueville, J., Paumgartner, G., and Howard, M. M.: Indocyanine green clearance as a test for hepatic function. Evaluation by dichromatic ear densitometry. J.A.M.A., *200*:236, 1967.
20. Leevy, C. M., Tamburro, C., and tenHove, W.: Ethanol oxidizing enzymes and response to liver injury. *In* Vandenbroucke, J., DeGroote, J., and Standaert, L. O., eds.: Liver Research. Tijdschrift voor Gastroenterologie, Antwerpen, Belgium, 1967, p. 71.
21. Leevy, C. M., tenHove, W., and Howard, M. M.: Mesenchymal cell proliferation in liver disease of the alcoholic. J.A.M.A., *187*:598, 1964.
22. Leevy, C. M., Zinke, M. R., Baber, J., and Chey, W. Y.: Observations on the influence of medical therapy on portal hypertension in hepatic cirrhosis. Ann. Int. Med., *49*:837, 1958.
23. Ning, M., Baker, H., and Leevy, C. M.: Reduction of glutamic pyruvic transaminase in pyridoxine deficiency in liver disease. Proc. Soc. Exp. Biol. Med., *121*:27, 1966.
24. Popper, H., Elias, H., and Petty, D. E.: Vascular pattern of the cirrhotic liver. Amer. J. Clin. Path., *22*:717, 1952.
25. Porta, E. A., Hartroft, W. S., Gomez-Dumm, C. L. A., and Koch, O. R.: Dietary factors in the progression and regression of hepatic alterations associated with experimental chronic alcoholism. Fed. Proc., *26*:1449, 1967.
26. Ratnoff, O. D., and Patek, A. J., Jr.: Natural history of Laennec's cirrhosis of liver: Analysis of 386 cases. Medicine, *21*:207, 1942.
27. Reynolds, T. B., Redeker, A. G., and Kuzma, O. T.: Role of alcohol in pathogenesis of alcoholic cirrhosis. *In* McIntyre, N., and Sherlock, S., eds.: Therapeutic Agents and the Liver. Philadelphia, F. A. Davis Co., 1965, p. 131.
28. Rubin, E., and Lieber, C. S.: Alcohol-induced hepatic injury in non-alcoholic volunteers. New Eng. J. Med., *278*:869, 1968.
29. Thomson, A., Baker, H., and Leevy, C. M.: Thiamine absorption in alcoholism. Amer. J. Clin. Nutr., *21*:537, 1968.
30. Zieve, L.: Pathogenesis of hepatic coma. Arch. Int. Med., *118*:211, 1966.

Veterans Administration Hospital
Tremont Avenue & S. Centre Street
East Orange, New Jersey 07019

A Rational Program for the Diagnosis and Treatment of Bleeding Esophageal Varices

HAROLD O. CONN, M.D.*

JOHN A. SIMPSON, M.D.**

Hemorrhage from esophageal varices is one of the most formidable emergencies in medicine. The mortality associated with variceal hemorrhage has averaged 67 per cent at the large medical centers in this country.[9, 21, 36, 42, 44, 53, 69]

There are many reasons for this awesome death rate. First, variceal bleeding usually occurs in decompensated cirrhotic patients who do not well withstand the consequences of massive hemorrhage. Cirrhotic patients often have abnormal coagulation, due either to impaired hepatic synthesis of clotting factors, to the thrombocytopenia of hypersplenism, or to circulating fibrinolysins or anticoagulants. Hemorrhage may be so massive that some patients become exsanguinated even in the absence of clotting disorders. Some patients die as a consequence of the breakdown of blood in the gastrointestinal tract, despite control of the hemorrhage. Others develop delerium tremens at a critical time. Electrolyte abnormalities are often present and include hyponatremia, hypokalemia, and hypomagnesemia as well as respiratory and metabolic alkalosis. Second, the source of the hemorrhage is not readily evident. Approximately one third of cirrhotic patients with upper gastrointestinal hemorrhage have bled from sites other than varices.[6, 15] This incidence is too high to permit the assumption that all cirrhotic patients are bleeding from varices, since the therapy of hemorrhage from varices is so different from that of nonvariceal hemorrhage. Third, each of the methods

---

From the Veterans Administration Hospital, West Haven, and the Department of Medicine, Yale University School of Medicine, New Haven, Connecticut

*Chief, Hepatic Research Laboratory, Veterans Administration Hospital; Associate Professor of Medicine, Yale University School of Medicine

**Clinical Instructor, Yale University School of Medicine

These investigations were supported in part by grants from the Irwin Strasburger Memorial Medical Foundation and The Stratfield Fund.

of treating bleeding esophageal varices is in itself dangerous. Conservative measures used in the management of variceal hemorrhage, such as balloon tamponade of the esophagus, gastric cooling, or vasopressin, are each associated with significant hazards. More radical forms of therapy, which include transesophageal ligation of varices and emergency portacaval anastomosis, both carry high operative mortality rates. Fourth, the accepted form of definitive treatment, the creation of a portal-systemic anastomosis, has an elective operative mortality of 10 to 15 per cent.[24, 58] Finally, portacaval anastomoses may be complicated by portal-systemic encephalopathy which may directly or indirectly cause death.[54]

This brief sketch paints a grim but realistic picture of the bleeding cirrhotic patient. When one considers the array of metabolic abnormalities and iatrogenic dangers that face the patient, it is surprising that even a third survive. On the other hand, many of the defects outlined are correctable and most of the therapeutic hazards are avoidable. With prompt and precise diagnosis, rational therapy can be instituted.

It is the purpose of this paper to review in detail the diagnosis and management of hemorrhage from esophageal varices, to evaluate each of the accepted diagnostic and therapeutic measures, and to outline a logical, effective program. Whenever possible this program is based on data obtained from controlled investigations. Often one must rely on less precise information; we have, however, attempted to choose the most objective information available. Many of the data have been collected at the West Haven Veterans Administration Hospital (WHVAH) during active investigations of this problem over the past decade. The program to be outlined is designed primarily for patients of the type seen at urban hospitals in this country—predominantly those with alcohol-nutritional Laennec's cirrhosis. Consequently, it is based primarily on observations made at American medical centers, rather than on studies from foreign institutions where cirrhosis of other types may predominate.[68] The program was devised to take advantage of the experience and enthusiasm of our staff; we appreciate that major modifications might be necessary at other institutions, where the skills and inclinations of the staff are differently oriented. Finally, our program has evolved as new and better information has become available and as our experience has dictated; certainly, it will continue to do so.

Although we have divided the management of bleeding varices into discrete categories, such as emergency management, diagnosis, and definitive therapy, such divisions are arbitrary and overlapping. Although each of these goals successively dominates one phase of management, all proceed together. Furthermore, the program is flexible and must be tailored to satisfy the needs of the individual patient.

EMERGENCY MANAGEMENT

This aspect of treatment is designed to correct as soon as possible those abnormalities which threaten the patient's life, and to maintain the patient in optimal condition until more definitive action can be undertaken. It consists specifically of the administration of whole blood or other fluids to correct or prevent shock and to maintain the hematocrit at a reasonable level. It insures an adequate airway. Finally, it is the phase in which nonspecific therapy is begun and in which preliminary diagnostic procedures may be initiated. During this phase, for example, one may confirm the presence of fresh blood in the stomach and remove this potentially toxic material by ice water lavage.

SUPPORTIVE MANAGEMENT

This aspect of treatment means many things for many patients. It may involve simply the administration of appropriate amounts of parenteral fluids, or it may require correction of specific electrolyte abnormalities. Routinely, vitamins, particularly B-complex, C, and K, are administered along with folic acid to assure availability of these substances. Sometimes paracentesis is required in patients with tense ascites to relieve pain or respiratory embarrassment and, incidentally, to decrease portal venous pressure[18] and gastroesophageal reflux.[65] Antibiotics may be indicated to combat respiratory or other bacterial infection.

Blood Transfusions. The single most important factor in the supportive management of upper gastrointestinal hemorrhage is blood replacement. In the cirrhotic patient the blood administered should be fresh. In cirrhosis many abnormalities of coagulation occur, some of which result in abnormal bleeding and interfere with attempts to control hemorrhage.[52] The liver synthesizes many clotting factors, some of which are vitamin K-dependent: prothombin, factor VII (proconvertin), factor IX (plasma thromboplastin component), and factor X (Stuart). Others, including fibrinogen, factor V (proaccelerin), and factor XIII (fibrin-stabilizing factor), are made in the liver, but are not vitamin K-dependent. In addition, thrombocytopenia may be present, either as a consequence of hypersplenism or secondary to folic acid deficiency. Finally, patients with cirrhosis may occasionally have circulating anticoagulants or fibrinolysins.[60]

The multiplicity of these clotting defects demands that cirrhotic patients with gastrointestinal hemorrhage be screened to identify clotting abnormalities. This can be accomplished by quantifying prothrombin time, partial thromboplastin time, and platelets. In the emergency situation or when a competent clotting laboratory is not available, most of these problems can be avoided by giving fresh blood collected in plastic bags or silicone-coated bottles within 5 hours of administration. Fresh blood provides platelets and many of the other critical substances, particularly factors V, VII, and IX. Certainly blood older than 5 days should not be administered, since factor V, which is usually deficient in cirrhosis, is present in small amounts in older blood. Fresh frozen plasma may also provide replacement of some of these hepatically synthesized factors.[66] Specific deficiencies may be corrected by platelet transfusions or platelet-rich plasma, and by concentrated prothrombin complexes.

Prevention of Ammonia Intoxication. One of the first and most important aspects of the management of gastrointestinal hemorrhage in cirrhosis is the need to prevent ammonia intoxication. Bacterial action on blood in the intestinal tract generates toxic amounts of ammonia which bypass the liver through portal-systemic collaterals and enter the systemic circulation. The increase in blood urea nitrogen, which frequently accompanies gastrointestinal bleeding, also provides substrate for bacterial ammonia production. Furthermore, the frequent occurrence in decompensated cirrhosis of respiratory and metabolic alkalosis, the latter associated with potassium deficiency, potentiates ammonia toxicity.[39, 56]

This complication may be ameliorated or prevented by evacuation of the gastrointestinal tract and by aspiration of blood from the stomach. Vigorous catharsis should be carried out along with repeated cleansing enemas. The mechanical removal of this potential source of ammonia, which is the single most important feature of treatment, may be aided by the administration of neomycin or other nonabsorbable antibiotics orally and enematically. These procedures, however, tend to increase the potassium deficit and should be accompanied by the parenteral administration of potassium chloride. Serial measurements of the blood ammonia, pH, and serum electrolytes will permit correction of these abnormalities. Early attention to these details may avoid the difficulties and complications of treating a comatose patient.

DIAGNOSIS

The definitive diagnosis of the site of hemorrhage in bleeding cirrhotic patients is a many-faceted thing. Palmer and his associates have emphasized that cirrhotic patients often bleed from gastrointestinal sites other than varices, and they have demonstrated the need for, and advantages of, a vigorous diagnostic approach to this problem.[46] We adhere to this principle, although we are inclined to modify the order of examinations to suit the individual situation.

HISTORY AND PHYSICAL EXAMINATION Questioning and examination of the patient provide important information about the presence or absence of cirrhosis, about the presence and degree of portal hypertension, about the recency and magnitude of the hemorrhage, and about potential sites of bleeding other than varices. This information may be complemented by aspiration of the gastric contents and examination of the stool. Although helpful, these leads are rarely definitive, and serve primarily as guides for arranging the most rewarding order of diagnostic inquiry.

EMERGENCY ESOPHAGOSCOPY. The rationale of emergency esophagoscopy is predicated on the assumption that when performed during active bleeding this examination can distinguish esophageal hemorrhage from all other sites of bleeding. Esophagoscopy permits visualization of bleeding esophageal lesions, such as varices, ulcers, acute erosive esophagitis, mucosal tears, and tumors, and, occasionally, of gastric lesions which fall into the field of vision as the esophagoscope passes through the carioesophageal junction (Fig. 1). It does not allow the precise diagnosis of other common bleeding sites, such as gastric,

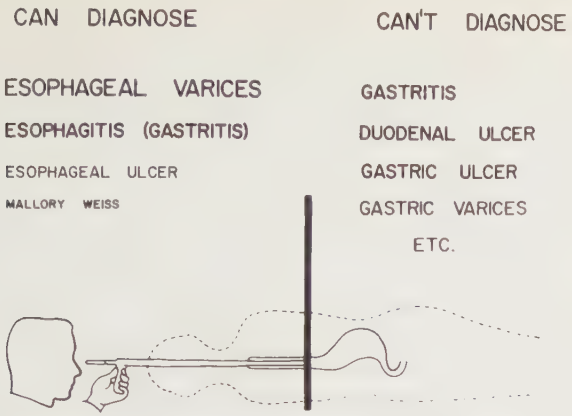

Figure 1. Rationale of emergency esophagoscopy. The esophagoscope can detect bleeding lesions from the pharynx to the cardioesophageal junction, and, occasionally, can identify gastric sites. The diagnosis of most subdiaphragmatic lesions, including gastric varices, can be made only inferentially by esophagoscopy.

duodenal, or marginal ulcers, gastric neoplasia, gastritis, or gastric varices, which are lumped together by exclusion as "nonvariceal hemorrhage." The rationale of this technique requires that physicians realize the diagnosis cannot be made correctly in patients with bleeding gastric varices. Therapeutically this may prove embarrassing, since the treatment of gastric varices differs greatly from the management of other gastric bleeding sites. Despite the handicap and inherent difficulties in ascertaining the source of bleeding during active hemorrhage, this technique has proved effective in our experience.

Emergency esophagoscopy has been attempted on 151 occasions in patients with gastrointestinal hemorrhage at the WHVAH during the past 10 years. Three fourths of the patients had cirrhosis; the others had hepatomegaly or there were other reasons to suspect an esophageal bleeding site. In 142 the examination was performed successfully (94 per cent). The site of hemorrhage was considered proved in 78 patients by criteria previously described.[11] Varices were the source of hemorrhage in about two thirds of the cirrhotic patients; peptic ulcers were responsible for bleeding in half of the noncirrhotic patients (Table 1). In four

Table 1. *Proved Sites of Hemorrhage in Patients Examined by Esophagoscopy*

BLEEDING SITE	CIRRHOTIC PATIENTS	NONCIRRHOTIC PATIENTS	TOTAL
Esophageal-gastric varices	37	1	38
Esophagitis-gastritis	8	5	13
Peptic ulcer	10	11	21
Miscellaneous	3	3	6
All sites	58	20	78

Table 2. *Accuracy of Esophagoscopic Diagnoses*

ESOPHAGOSCOPIC OBSERVATION	NO. OF PATIENTS	DIAGNOSIS CORRECT	DIAGNOSIS INCORRECT	DIAGNOSTIC ACCURACY
Bleeding esophageal varices	28	28	0	100%
No esophageal varices	37	35	2	95%
Nonbleeding esophageal varices	13	5	8	38%
Total	78	68	10	87%

instances, the esophagoscope could not be passed into the esophagus, and in five, adequate visualization of the esophagus was not possible. Virtually all of these examinations were performed by the same endoscopist. In all instances the Eder-Hufford esophagoscope was used. Examinations were performed under topical anesthesia with small doses of meperidine (Demerol) (25 mg.) and atropine preoperatively. In patients in whom hepatic precoma was present, no medications were used.

Considering the critical condition of these patients, the morbidity was negligible.[17] One patient died of cardiac arrest during esophagoscopy. No cause for the sudden death was found at autopsy. Another patient developed a convulsive seizure which necessitated discontinuation of the examination. There were no perforations of the esophagus or other complications of endoscopy. In only one instance did the procedure appear to increase the rate of bleeding.

The endoscopic diagnosis was correct in 68 of 78 examinations (87 per cent) in which the site of hemorrhage was proved. The endoscopic findings fell naturally into three groups (Table 2). First was a group of 28 patients in whom bleeding esophageal varices were seen. The esophagoscopic diagnosis was confirmed in all 28 of these patients (100 per cent). The second group included 37 patients in whom varices were not present and in whom the bleeding was considered to be coming from "nonvariceal" lesions below the cardioesophageal junction. These diagnoses were proved correct in 35 of the 37 patients (95 per cent). In the third group were 13 patients in whom varices were seen, but were not thought to be the cause of the bleeding. The implied diagnosis of a nonvariceal bleeding site was correct in only 5 of these 13 patients (38 per cent).

It seems clear from these data that emergency esophagoscopy alone can rapidly and reliably distinguish variceal from other bleeding lesions in most patients. For this reason we feel that it should be the diagnostic keystone in patients in whom this differential diagnosis is pertinent. When esophagoscopy demonstrates bleeding varices or indicates that varices are not present, appropriate therapy may be undertaken with confidence. When this examination does not give a definitive answer, such as in situations in which nonbleeding varices are seen, further diagnostic measures must be undertaken.

It should be emphasized that emergency esophagoscopy is most valuable when performed during active hemorrhage. Although the endoscopic diagnosis of varices, like all other subjective diagnostic methods, is susceptible to error,[12, 14] the recognition of a bleeding varix is probably easier than the more subtle differentiation of esophageal varices from mucosal folds in the nonbleeding situation. To delay this examination until bleeding is controlled defeats the very essence of this functional diagnostic tool.

EMERGENCY GASTROSCOPY. Gastroscopy has been a useful adjunct in the diagnosis of gastrointestinal hemorrhage for some years.[6, 13, 16] The recent availability of a fiberoptic gastroscope, which can be passed through the conventional esophagoscope, allows both examinations to be accomplished expeditiously and with minimal discomfort to the patient. Emergency gastroscopy may provide identification of many gastric bleeding sites including gastric varices. Although our experience with this technique is limited, other authors have found it to be effective for this purpose.[16] The gastroscope is more limited in its diagnostic capability during active hemorrhage than the more simple, lensless esophagoscope by virtue of its lens system, which may become smeared by blood. For this reason gastroscopy may be of greater value after bleeding has subsided. Hemorrhage, particularly from erosive gastritis, is often slowed or stopped by ice water lavage, which should be used copiously before endoscopy.

The gastroscopic differentiation of varices from mucosal folds[14] may be especially difficult with fiberoptic instruments, which do not transmit color without distortion.[10] The demonstration of erosive gastritis, or its exclusion, is probably the most useful role of gastroscopy. In this manner gastroscopy can complement and enhance the diagnostic value of the esophagoscopic and radiologic examinations.

BARIUM CONTRAST EXAMINATION OF THE UPPER GASTROINTESTINAL TRACT. In patients in whom endoscopic examinations have failed to detect the bleeding source or have suggested a subdiaphragmatic lesion, an upper gastrointestinal series may show the responsible lesion. There is little need for a barium esophagogram in patients who have already undergone esophagoscopy, since the radiologic demonstration of esophageal varices, whether confirmatory or contradictory, does not add to knowledge of the bleeding site. This examination can most profitably be directed toward careful evaluation of the stomach and duodenum. Although the mere demonstration of a potential bleeding site is poor evidence that it has bled, such information in a patient already shown to have a normal esophagus endoscopically provides a reasonable basis for making therapeutic decisions. The failure to demonstrate any upper gastrointestinal lesion in a patient with endoscopic diagnosis of nonbleeding varices and no erosive gastritis suggests strongly that the varices are the most likely source of the bleeding. Radiologic diagnoses are, of course, inferential and must be considered in terms of the whole clinical and laboratory picture. Obviously, in patients whose history suggests the presence of a peptic ulcer, for example, radiologic examination may often be performed first. Once again such diagnostic techniques ought to be performed by advocates of the procedure. If a radiologist, for example, believes that emergency barium studies of the gastrointestinal tract in critically ill patients whose stomachs are full of blood are useless, his examinations performed under such circumstances are likely to be useless.

OTHER TESTS. The *blood ammonia concentration* has enjoyed brief popularity as a diagnostic test in gastrointestinal bleeding.[35] Blood ammonia levels are usually elevated in cirrhotic patients with gastrointestinal hemorrhage and normal in noncirrhotic patients. Increased ammonia levels indicate that a cirrhotic patient may have bled, but they cannot identify the site of bleeding.[3, 67] Blood retained in the gastrointestinal tract from varices, ulcer, or any other site may increase blood ammonia levels. Indeed, blood ingested by nonbleeding cirrhotic patients causes elevated blood ammonia concentration.[78]

Similarly *bromsulphalein* (BSP) *retention* is useful only in suggesting or excluding the presence of liver disease. Nonspecific elevations of BSP in the absence of serious liver disease may, however, prove misleading.[3]

Rousselot and his colleagues have reported that the *splenic pulp pressure* during or shortly after gastrointestinal hemorrhage is a useful diagnostic index of the source of bleeding.[59] They found that splenic pulp pressures greater than 300 mm. of saline were invariably associated with hemorrhage from varices, while pressures of less than 250 mm. occurred in patients with other bleeding sites. These findings imply that cirrhotic patients with portal hypertension do not bleed from peptic ulcers or gastritis, despite a high incidence of these disorders. Although our observations of these surprising phenomena are limited, others have reported contradictory data.[25] Further investigations of splenic pulp pressure in gastrointestinal hemorrhage are needed in patients in whom the site of bleeding is established unequivocally.

A therapeutic trial of the *Sengstaken-Blakemore tube* (SBT) is often cited as a useful diagnostic test. Although the premise that only variceal bleeding will be controlled by the insertion of this instrument is reasonable, it is unverified and often incorrect.[9] The diagnostic failure of the SBT cannot be attributed to the tube itself, but, paradoxically, to the efficacy of the gastric lavage which accompanies its use. Ice water lavage which is carried out to empty the stomach or to determine whether the SBT is controlling the bleeding, is itself an effective form of therapy for gastrointestinal bleeding, particularly gastritis. Furthermore, the passage of the SBT is frankly dangerous,[13] and it seems irrational to use a diagnostic method which is both unreliable and unsafe.

Various modifications of the string test, which may be of suggestive diagnostic aid in chronic gastrointestinal bleeding, offer little help during active massive hemorrhage.

The recent introduction of selective arteriography in determining the site of hemorrhage is an exciting development that deserves careful evaluation.[2]

TREATMENT OF HEMORRHAGE

The goal in the treatment of hemorrhage from esophageal varices is control of bleeding and preservation of life until corrective therapy can be undertaken. In addition to the nonspecific measures, such as blood transfusion, a number of specific methods are available to control hemorrhage, including mechanical, pharmacologic, and hypothermic techniques. Each is associated with hazards which can be justified by the excessive mortality associated with hemorrhage from varices. Our program, which is based on our estimates of the benefits and risks of each of these types of treatment, starts with the most benign and proceeds in order to those with lower therapeutic ratios.

Vasopressin Therapy. The form of treatment which is most simple and least dangerous, and, therefore, which offers the best therapeutic bargain, is the administration of pharmacologic agents which decrease splanchnic blood flow and portal venous pressure. Vasopressin has been extensively and effectively used for this purpose during the past decade.[31, 37, 61, 63] Merigan and his associates, in a carefully controlled clinical trial, demonstrated that a single dose of vasopressin promptly stopped variceal hemorrhage in half their treated patients.[37] They reported, however, that the mortality was equally high in both the treated and untreated groups, and for this reason the use of vasopressin has fallen into disfavor. This reasoning appears to us to be fallacious; it is like discarding penicillin for the treatment of pneumococcal pneumonia because a single dose, although transiently beneficial, does not improve the prognosis. Multiple doses of penicillin, however, cure pneumococcal pneumonia, and multiple doses of vasopressin can control hemorrhage from varices in a large fraction of bleeding patients.

Our experience with vasopressin in 40 episodes of hemorrhage in 35 patients treated at this hospital over the past 8 years is shown in Table 3. These data include all patients proved to be bleeding from varices who were treated with vasopressin. No other specific therapy was administered simultaneously. Control of bleeding was defined as the absence of blood from the stomach for a period of at least 24 hours, determined by intermittent gastric aspiration. Fourteen of the 40 hemorrhages (35 per cent) were controlled by vasopressin. Analysis of the data revealed that bleeding was controlled in only 2 of 12 patients (17 per cent) who received single or sporadic doses of vasopressin, but in 12 of 28 (43 per cent) who received more intensive courses of therapy ranging from 2 to 10 doses. Although survival was better in those patients in whom multiple doses were used, the significance of the survival data is not clear, since observations were not controlled and many other factors were involved.

When used, 20-unit doses of vasopressin or posterior pituitary extract should be diluted with 20 to 30 ml. of saline and administered intravenously by syringe over 10 to 15 minutes. These doses may be given at 1 to 2-hour intervals. It is important that the effect of the drug be monitored by frequent aspirations of the gastric contents through an indwelling tube. After bleeding has been controlled for 3 to 4 hours the frequency of administration may be rapidly tapered and plans made for definitive therapy. If vasopressin is unsuccessful after three or four doses, it should be abandoned in favor of other forms of treatment.

Vasopressin, however, is not without hazard. It induces a rise in

Table 3. *Result of Vasopressin on Hemorrhage from Varices*

TREATMENT GROUP	PATIENTS	HEMORRHAGES	HEMORRHAGES CONTROLLED		SURVIVED HOSPITAL ADMISSION	
			NUMBER	PER CENT	NUMBER	PER CENT
Single dosage*	12	12	2	17%	0	0%
Multiple dosage†	23	28	12	43%	10	43%
Total	35	40	14	35%	10	29%

*Vasopressin administered once, or on several occasions sporadically.

†Vasopressin administered as a series of two or more doses until hemorrhage controlled or until vasopressin treatment abandoned.

blood pressure due to peripheral vasoconstriction, which should not be misinterpreted in the hypotensive patient. In addition it is contraindicated in patients with coronary artery disease because of its coronary vasoconstrictive properties. We have observed one patient who developed a fatal myocardial infarction shortly after the administration of vasopressin. When vasopressin is administered it should, therefore, be monitored electrocardiographically and amyl nitrite or other fast-acting coronary dilators should be at the bedside.

ESOPHAGOGASTRIC HYPOTHERMIA. A nontamponading gastric balloon through which is circulated an alcohol-water solution at 0 to 14° C. has been reported as beneficial in controlling upper gastrointestinal bleeding from a number of causes.[73] Reports of its use in hemorrhage from varices have been limited but encouraging.[55, 72] Like posterior pituitary extract and esophageal tamponade, its effects are usually transient.[72] It may, however, offer temporary control of hemorrhage from varices while the patient is being prepared for more definitive therapy. Our limited personal experience with this technique indicates that it may transiently control bleeding, but that it is not free of serious hazards.

A simple form of therapy which is often overlooked is ice water lavage of the stomach. This technique, which is used to prepare patients for emergency endoscopy, often appears to slow bleeding and occasionally to stop it entirely. This is particularly true in patients with gastritis, but also occurs in patients bleeding from esophageal varices. It should be carried out using large volumes of ice water and a large gastric tube through which clots can be aspirated.

ESOPHAGEAL BALLOON TAMPONADE. During the past 20 years, since Sengstaken and Blakemore described their ingenious tube (SBT) for the treatment of bleeding varices,[62] esophageal tamponade has become the most widely used form of therapy. Although the SBT controls bleeding in half to three fourths of the patients in whom it is used, its effect is often transient, and recurrences of bleeding are common.[36, 71] Most disturbing is the high incidence of serious hazards attending its use. At this hospital, we have observed fatal complications in about 20 per cent of the patients in whom it was used, despite awareness of the hazards and intensive attempts to avoid them. The most common cause of death was vomiting with the inflated SBT in place, resulting in massive pulmonary aspiration. This problem often occurred during the initial passage of the tube. The hazards of balloon tamponade have recently been described in detail[13] and will not be discussed further here.

We believe that this instrument is too dangerous for routine use in all patients with bleeding varices. It should be reserved for those patients proven unequivocally to be bleeding from esophageal varices, in whom bleeding continues despite conservative therapy and in whom surgical intervention is considered impossible. In such probably fatal situations, one is justified in taking the high risks associated with its use. When the SBT is used it should be placed and maintained in an intensive care unit by experienced personnel who are aware of its hazards and their prevention and treatment. Prophylactic tracheostomy or endotracheal intubation prior to passage may prevent some of the complications. Modifications of the SBT by Linton[33] and Nachlas[40] theoretically provide safer balloon tamponade, but adequate data about their efficacy and safety are not available.

DEFINITIVE THERAPY

Definitive treatment of patients who have bled from esophageal varices is portal decompression, usually portacaval anastomosis. Although this operation is considered the treatment of choice by almost all authorities, its efficacy has never been established by controlled clinical trial.[24] Some authors have soberly and thoughtfully challenged this prevailing opinion.[7, 41] The ongoing Veterans Administration Cooperative Study[29] has obtained preliminary data which for the first time provide an objective rationale for this standard form of therapy.[28]

At most hospitals portal-systemic shunts are performed on survivors after they have recovered from the effects of the hemorrhage and after they have satisfied arbitrary criteria of operability. Often these criteria are sufficiently stringent to exclude a large fraction of the survivors.[4, 32, 33, 75] In view of the high incidence of recurrent hemorrhage and the poor prognosis associated with it, we have tended to ignore conventional arbitrary criteria of operability and to recommend portal decompression in practically all survivors of bleeding varices. Since the time of recurrence of bleeding cannot be predicted, we are opposed to delaying surgery until maximal hospital benefit has been achieved, a goal which may take months. We favor performing surgery within a week of hemorrhage unless the patient's hepatic status is obviously deteriorating. When variceal hemorrhage recurs in patients awaiting surgery, we feel that immediate portacaval shunt is indicated.

Emergency Portacaval Anastomosis. Elective portal decompression is available to only a small fraction of patients who have bled from esophageal varices (Fig. 2). Patients who die of hemorrhage or its consequences, of course, exclude themselves from further therapeutic measures. Some of the survivors are excluded as poor operative risks. At this hospital only one fourth of 101 patients with variceal bleeding survived hemorrhage, and fewer than one sixth were considered operative

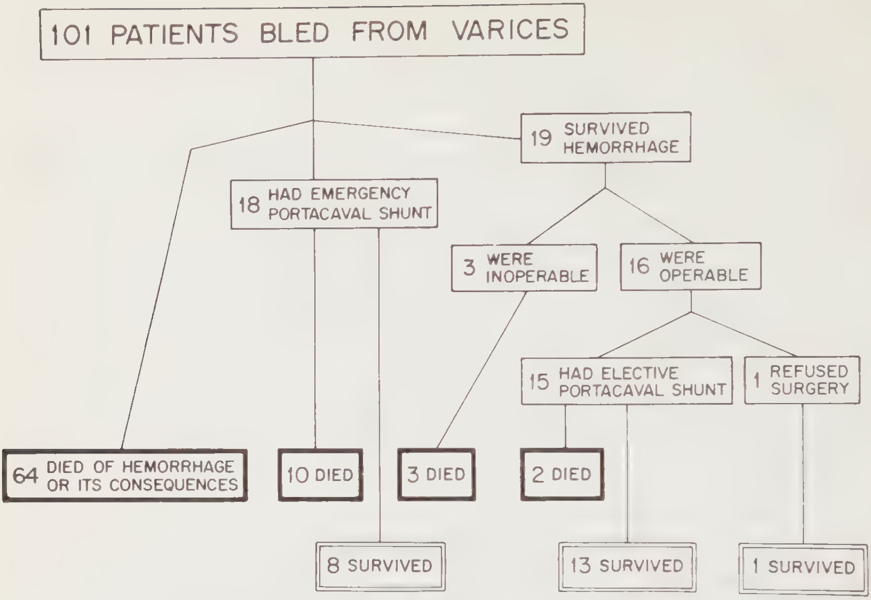
101 PATIENTS BLED FROM VARICES
19 SURVIVED HEMORRHAGE
18 HAD EMERGENCY PORTACAVAL SHUNT
3 WERE INOPERABLE
16 WERE OPERABLE
15 HAD ELECTIVE PORTACAVAL SHUNT
1 REFUSED SURGERY
64 DIED OF HEMORRHAGE OR ITS CONSEQUENCES
10 DIED
3 DIED
2 DIED
8 SURVIVED
13 SURVIVED
1 SURVIVED

Figure 2. Prognosis of bleeding from esophageal varices. Almost two thirds of a group of 101 patients died of hemorrhage or its consequences. One fifth had emergency portacaval anastomoses and half of these died. One fifth survived hemorrhage, most of whom were considered reasonable operative risks. Most of those who underwent elective portacaval anastomosis survived. The overall mortality was 79 per cent.

candidates for elective portacaval shunts (Fig. 2). The great majority of the deaths occurred from exsanguination, consequences of prolonged or recurrent hemorrhage, or complications of therapy.

The concept of emergency portacaval anastomosis was developed in an attempt to salvage those patients who may have been reasonable operative risks shortly after hemorrhage had occurred, but who subsequently deteriorated as bleeding continued or recurred. During the past 10 years, numerous authors have reported their experience with emergency portacaval shunts in cirrhotic patients with actively bleeding esophageal varices (Table 4). Two clear-cut conclusions are apparent from these reports of more than 300 patients. First, emergency portacaval anastomosis promptly controls hemorrhage from varices. Second, the operative mortality, which averaged 39 per cent (range 20 to 71 per cent), appeared considerably lower than the 66 per cent reported for variceal hemorrhage treated by other methods.[8, 36, 42, 44, 53, 69] The patients reported in these papers represent heterogeneous groups presented for different purposes by authors of divergent persuasions. Although they appear to represent the full spectrum of cirrhosis, it is impossible to appreciate the factors which influence the selection of patients for surgery or data for publication.

To determine unequivocally the value of emergency portacaval anastomosis, prospective, randomized clinical trials are required. No such data are available, although at least one such study is in progress.

Table 4. *Results of Emergency Portacaval Anastomosis*

SENIOR AUTHOR AND REFERENCE	YEAR OF PUBLICATION	NO. OF PATIENTS	NO. WHO DIED POSTOPERATIVELY*	OPERATIVE MORTALITY IN PER CENT
Rousselot[57]	1960	10	4	40%
Wantz[74]	1961	34	14	41%
Mikkelsen[38]	1962	34	11	32%
Shaldon[64]	1962	10	2	20%
Brick[6]	1964	18	7	39%
Ekman[19]	1964	17	4	24%
Peskin[49]	1964	13	3	23%
Preston[51]	1965	25†	11	44%
Weinberger[77]	1965	29	8	28%
Hermann[27]	1966	14	10	71%
Adson[1]	1967	19	5	26%
Foster[20]	1967	22	12	55%
Orloff[45]	1967	40	19	48%
Conn (present paper)	1968	17‡	9	53%
Total		302	119	39%

*Postoperative deaths include all patients who died during hospital admissions, of if that data not available, all patients who died within 30 days of surgery.

†Includes one patient who bled from spleen and had splenorenal anastomosis.

‡Includes one patient who died after unsuccessful portacaval shunt and excludes one patient who died of hepatoma after successful shunt.

In the absence of controlled data, one is tempted to accept the lower operative mortality of emergency portacaval anastomosis rather than the higher mortality associated with conventional therapy, despite the well-known dangers of comparing two sets of uncontrolled data.[24] These data are particularly attractive, since this aggressive approach provides prompt control of hemorrhage as well as definitive portal decompression. Furthermore, our own uncontrolled observations also suggest that emergency portacaval shunts offer greater survival than other forms of treatmen ($p < 0.025$) (Table 5).

Why is emergency portacaval anastomosis such an attractive concept? One may reason that the optimal time for performing portal decompression is 24 hours *before* the patient bleeds from varices. Such omniscient predictions are beyond the skills of present-day physicians. It is often true, however, that the cirrhotic patient, during the first 24 hours

Table 5. *Comparison of Emergency Portacaval Anastomosis With Other Forms of Therapy of Bleeding Esophageal Varices*

GROUP	NO. OF PATIENTS IN GROUP	NO. OF PATIENTS WHO LEFT HOSPITAL ALIVE	PER CENT SURVIVAL
Emergency portacaval anastomosis	17*	8	44%
All other forms of therapy	83	14	17%
Total	100	22	22%

*Excludes 1 patient who had hepatoma which caused death.

after hemorrhage from esophageal varices has begun, is in the best physical condition he will ever again achieve. If so, the ideal time for emergency portacaval anastomosis is as soon as the diagnosis of bleeding varices is established. Until good data to the contrary become available, it is our opinion that emergency portacaval anastomosis should be undertaken in practically all cirrhotic patients in whom unequivocal proof of bleeding varices has been obtained. The only absolute contraindication to surgery is the presence of severe hepatic parenchymal or renal decompensation; ascites per se is not a contraindication. The greater risk of surgery in decompensated cirrhosis appears to be balanced by the terrible prognosis of continued hemorrhage in such patients.

PROPHYLACTIC PORTACAVAL ANASTOMOSIS. A logical extension of therapeutic portacaval anastomosis in patients who have already bled from varices is prophylactic portacaval anastomosis to prevent hemorrhage. Since the mortality of the first hemorrhage from varices is so high and since portacaval anastomosis can effectively prevent hemorrhage, it would appear reasonable to perform prophylactic portal decompression in cirrhotic patients with esophageal varices. Three independent controlled investigations, however, have found that prophylactic portacaval shunts did not increase survival.[12a, 22, 30] In fact, the surgically treated patients fared less well than the unoperated control subjects in each of the three studies. Re-evaluation of our data showed that overt ascites was almost always present prior to variceal hemorrhage. On the basis of these observations a new controlled investigation of prophylactic portacaval anastomosis was undertaken in cirrhotic patients with esophageal varices and ascites. Preliminary results obtained in approximately 70 patients have shown (a) that patients with overt ascites are particularly prone to bleed fatally from varices, (b) that portacaval anastomosis can be accomplished in such patients with reasonably low operative mortality, and (c) that prophylactic portacaval shunts virtually eliminate hemorrhage from varices.[12b] If these trends continue and are confirmed, it would appear that prophylactic portacaval anastomosis can enhance survival in selected cirrhotic patients with esophageal varices.

TRANSESOPHAGEAL LIGATION. We have accumulated little personal experience with transesophageal ligation of varices in the emergency management of esophageal bleeding as recommended by Linton and his associates.[33] It is our impression, along with Rousellot,[37] Mikkelsen,[38] and others, however, that the cumulative mortality of emergency transesophageal ligation of varices plus elective portacaval anastomosis subsequently, is greater than the mortality of emergency portacaval anastomosis alone.

OTHER FORMS OF THERAPY. For those patients judged not suited to major surgical intervention, other less traumatic measures may be considered. Total body hypothermia has been employed as an adjunct to conventional therapy with some success in desperately ill patients bleeding from varices or other sites.[23] Macbeth has recommended sclerosing injection of esophageal varices, but there is little enthusiasm for this difficult procedure.[31] Dumont and his associates have found thoracic duct drainage to be a simple, effective method of rapidly reducing portal pressure and controlling variceal hemorrhage.[5, 17, 18] Recently Piccone and his colleagues have successfully decompressed the portal venous system by cannulating the umbilical vein and creating an extracorporeal or subcutaneous portosaphenous anastomosis.[50] These methods, none of which has yet been proved objectively to be beneficial, share the advantage of great potential gain at relatively small risk.

Warren and his colleagues have recently recommended a distal splenorenal anastomosis which they believe will stabilize hepatic function and may avoid portal-systemic encephalopathy.[76] Several groups have suggested the use of nonshunting procedures as more physiologic methods of treating patients with portal hypertension than portacaval shunts.[29] These techniques require objective evaluation.

SUMMARY

The prognosis of hemorrhage from esophageal varices is extremely grim. Despite the introduction of more accurate means of establishing the diagnosis, the widespread availability of blood transfusions, and the development of ingenious forms of therapy, the mortality associated with bleeding varices has not been appreciably decreased. Although these data may be more apparent than real, they permit one to paraphrase the popular beer advertisement: "We don't know what, but we must be doing something wrong." Indeed, we must be doing many things wrong. It is therefore necessary that we review critically each of the established diagnostic and therapeutic procedures in use, that we retain those that are effective and safe, and that we abandon those that are ineffective or dangerous. Based on a careful review of our own experience and on data from the literature, we have reached the following conclusions:

1. Emergency esophagoscopy provides a rapid, reliable, and safe method for establishing or excluding esophageal varices as the site of hemorrhage. It can serve as the keystone of diagnosis of upper gastrointestinal bleeding in the cirrhotic patient.
2. Vasopressin therapy offers a safe and simple way of controlling hemorrhage from varices in almost half of the patients in whom it is used. It can profitably be employed as the first step in treatment.
3. The Sengstaken-Blakemore tube appears too hazardous for routine use; it should be reserved for those patients whose poor prognosis justifies the greater risks inherent in its use.
4. Emergency portacaval anastomosis, despite a high operative mortality, appears to offer greater survival than occurs with more conservative forms of therapy—according to the available published data, which are, unfortunately, uncontrolled.
5. Prophylactic portacaval anastomosis, despite virtual elimination of hemorrhage from varices, does not increase survival in unselected cirrhotic patients. Preliminary studies suggest, however, that prophylactic portacaval anastomosis may decrease mortality in selected cirrhotic patients with a high risk of bleeding from esophageal varices.

ACKNOWLEDGEMENT

The authors express their appreciation to the many co-investigators and house officers who participated and assisted in the studies mentioned in this review.

REFERENCES

1. Adson, M. A.: Emergency portal-systemic shunts. Surg. Clin. N. Amer., *47*:887-898, 1967.
2. Baum, S., Nusbaum, M., Clearfield, H. R., Kuroda, K., and Tunen, H. J.: Angiography in the diagnosis of gastrointestinal bleeding. Arch. Int. Med., *119*:16-24, 1967.
3. Belkin, G. A., and Conn, H. O.: The blood ammonia concentration and bromsulphalein retention in upper gastrointestinal hemorrhage. New Eng. J. Med., *260*:530-534, 1959.
4. Blakemore, A. H.: The surgical treatment of cirrhosis of the liver. J. Chron. Dis., 2:70-90, 1955.
5. Bowers, W. F., McKinnon, W. M. P., Marino, J. M., and Culverwell, J. T. : Cannulation of the thoracic duct: Its role in the pre-shunt management of hemorrhage due to esophageal varices. Internat. Coll. Surg., *42*:71-76, 1964.
6. Brick, I. B., and Palmer, E. D.: One thousand cases of portal cirrhosis of the liver. Implications of esophageal varices and their management. Arch. Int. Med., *113*:501-511, 1964.
7. Cohn, R.: A skeptical evaluation of portacaval anastomosis for gastrointestinal hemorrhage in cirrhosis of the liver. Stanford M. Bull., *9*:231-235, 1951.
8. Cohn, R., and Blaisdell, F. W.: The natural history of the patient with cirrhosis of the liver with esophageal varices following the first massive hemorrhage. Surg. Gynec. Obstet., *106*:699-701, 1958.
9. Conn, H. O.: Hazards attending the use of esophageal temponade. New Eng. J. Med., *259*:701-707, 1958.
10. Conn, H. O., Binder, H., and Brodoff, M.: Fiberoptic and conventional esophagoscopy in the diagnosis of esophageal varices: A comparison of techniques and observers. Gastroenterology, *52*:810-818, 1967.
11. Conn, H. O., and Brodoff, M.: Emergency esophagoscopy in the diagnosis of upper gastrointestinal hemorrhage. A critical evaluation of its diagnostic accuracy. Gastroenterology, *47*:505-512, 1964.
12. Conn, H. O., Gordon, M. E., and Brodoff, M.: Red filters in the radiologic diagnosis of esophageal varices. Amer. J. Digest. Dis., *12*:1209-1215, 1967.
12a. Conn, H. O., and Lindenmuth, W. W.: Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. Interim results with suggestions for subsequent investigations. New Eng. J. Med. (in press).
12b. Conn, H. O., and Lindenmuth, W. W.: Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices and ascites. Experimental design and preliminary results. Amer. J. Surg. (in press).
13. Conn, H. O., and Simpson, J. A.: Excessive mortality with balloon tamponade. J.A.M.A., *202*:587-591, 1967.
14. Conn, H. O., Smith, H., and Brodoff, M.: Observer error in the endoscopic diagnosis of esophageal varices. New Eng. J. Med., 272:830-834, 1965.
15. Dagradi, A. E., Sanders, D., and Stempien, J.: The sources of upper gastrointestinal bleeding in liver cirrhosis. Ann. Int. Med., 42:852-855, 1955.
16. Dagradi, A. E., Stempien, S. J., and Owens, L. K.: Bleeding esophagogastric varices. An endoscopic study of 50 cases. Arch. Surg., *92*:944-947, 1966.
17. Denney, M. K., Lucas, C. E., and Read, R. C.: Significance of hematochylia in Laennec's cirrhosis. Arch. Surg., *92*:657-663, 1966.
18. Dumont, A. E., and Witte, M. H.: Thoracic duct cannulation: A new approach to the emergency treatment of bleeding esophageal varices. *In* Ellison, E. H., Friesen, S. R., and Mulholland, J. H., eds.: Current Surgical Management III. Philadelphia, W. B. Saunders Co., 1965, p. 264.
19. Ekman, C. A., and Sanblom, P.: Shunt operation in acute bleeding from esophageal varices. Ann. Surg., *160*:531-539, 1964.
20. Foster, J. H., and Vetto, R. M.: Fifteen years' experience with porta-systemic venous shunting operations. Amer. Surg., *33*:514-519, 1967.
21. Gould, W. M.: Hemorrhage from esophageal varices. A clinical study of 104 patients. M.D. thesis, Yale University School of Medicine, 1957.
22. Graceau, A. J., and the Boston Inter-Hospital Liver Group: The natural history of cirrhosis. II. The influence of alcohol and prior hepatitis on pathology and prognosis. New Eng. J. Med., *271*:1173-1179, 1964.
23. Gowen, G. F., and Lindenmuth, W. W.: General hypothermia for managing gastrointestinal hemorrhage. J.A.M.A., *175*:29-33, 1961.

24. Grace, N. D., Muench, H., and Chalmers, T. C.: The present status of shunts for portal hypertension in cirrhosis. Gastroenterology, *50*:684-691, 1966.
25. Green, L., Weisberg, H., Rosenthal, W. S., and Katz, D.: Evaluation of esophageal varices in liver disease by splenic-pulp pressure manometry, splenoportography and esophagogastroscopy. Amer. J. Digest. Dis., *10*:284-292, 1965.
26. Hassab, M. A.: Gastroesophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: Further studies with a report on 355 operations. Surg., *61*:169, 1967.
27. Hermann, R. E., Rodriguez, A. E., and McCormack, L. J.: Selection of patients for portal-systemic shunt. J.A.M.A., *196*:1039-1044, 1966.
28. Jackson, F. C.: Personal communication.
29. Jackson, F. C., Perrin, E. B., Jr., Dagradi, A. E., Smith, A. G., and Lee, L.: Clinical investigation of the portacaval shunt. I. Study design and preliminary survival analysis. Arch. Surg., *91*:43-54, 1965.
30. Jackson, F. C., Perrin, E. B., Smith, A. G., Dagradi, A. E., and Nadal, H. M.: A clinical investigation of the portacaval shunt. II. Survival analysis of the proplylactic operation. Amer. J. Surg., *115*:22-32, 1968.
31. Kehne, J. H., Hughes, F. A., and Gompertz, M. L.: The use of surgical pituitrin in the control of esophageal varix bleeding. Surg., *39*:917-925, 1956.
32. Large, A. M., and Johnston, C. G.: Evaluation of the portacaval shunt. Amer. J. Gastroenterol., *36*:15-31, 1961.
33. Linton, R. R., and Ellis, D. S.: Emergency and definitive treatment of bleeding esophageal varices. J.A.M.A., *160*:1017-1023, 1956.
34. Macbeth, R.: Treatment of oesophageal varices in portal hypertension by means of sclerosing injections. Brit. Med. J., 2:877, 1955.
35. McDermott, W. V., Jr.: A simple discriminatory test for upper gastrointestinal hemorrhage. New Eng. J. Med., 257:1161-1164, 1957.
36. Merigan, T. C., Jr., Hollister, R. M., Gryska, P. F., Starkey, G. W. B., and Davidson, C. S.: Gastrointestinal bleeding with cirrhosis: A study of 172 episodes in 158 patients. New Eng. J. Med., 263:579-585, 1960.
37. Merigan, T. C., Jr., Plotkin, G. R., and Davidson, C. S.: Effect of intravenously administered posterior pituitary extract on hemorrhage from bleeding esophageal varices: A controlled evaluation. New Eng. J. Med., *266*:134-135, 1961.
38. Mikkelsen, W. P.: Emergency portacaval shunt. Rev. Surg., *19*:141-148, 1962.
39. Mulhausen, R., Eichenholz, A., and Blumentals, A.: Acid-base disturbances in patients with cirrhosis of the liver. Med., *46*:185-189, 1967.
40. Nachlas, M. M.: The use of a triple-lumen single balloon in the diagnosis and treatment of massive upper gastrointestinal hemorrhage. Surg., *38*:667-674, 1955.
41. Nachlas, M. M.: A critical evaluation of venous shunts for the treatment of cirrhotic patients with esophageal varices. Ann. Surg., *148*:169-183, 1958.
42. Nachlas, M. M., O'Neil, J. E., and Campbell, A. J. A.: The life history of patients with cirrhosis of the liver and bleeding esophageal varices. Ann. Surg., *141*:10-23, 1955.
43. Olsen, A. M., and Moersch, H. J.: The role of gastroscopy in the diagnosis of upper gastrointestinal hemorrhage of obscure origin. Gastroenterology, *14*:292-299, 1950.
44. Orloff, M. J.: Emergency treatment of bleeding esophageal varices in cirrhosis. Curr. Prob. Surg., July 1966, pp. 13-28.
45. Orloff, M. J.: Emergency portacaval shunt: A comparative study of shunt, varix ligation and non-surgical treatment of bleeding esophageal varices in unselected patients with cirrhosis. Ann. Surg., *166*:456-478, 1967.
46. Palmer, E. D.: Further experiences with the vigorous diagnostic approach to upper gastrointestinal hemorrhage. Amer. J. Med. Sc., *233*:497-503, 1957.
47. Palmer, E. D., and Wirts, W. C.: Survey of gastroscopic and esophagoscopic accidents. Report of Committee on Accidents of the American Gastroscopic Society. J.A.M.A., *164*:2012-2015, 1957.
48. Panke, W. F., Rousselot, L. M., and Moreno, A. H.: Splenic pulp pressure as emergency test in differential diagnosis of acute upper gastrointestinal bleeding. Surg. Gynec. Obstet., *109*:270-278, 1959.
49. Peskin, G. W., Crichlow, R. W., Berggren, R. B., and Miller, L. D.: Portacaval shunt in the emergency treatment of variceal bleeding. Surg., *56*:800-805, 1964.
50. Piccone, V. A., and LaVeen, H. H.: Transumbilical portal decompression. Surg. Gynec. Obstet., *125*:66-72, 1967.
51. Preston, F. W., and Trippel, O. H.: Emergency portacaval shunt; use in patients with alcoholic cirrhosis. Arch. Surg., *90*:770-781, 1965.
52. Rapaport, S. I., Ames, S. B., Mikkelsen, S., and Goodman, J. R.: Plasma clotting factors in chronic hepatocellular disease. New Eng. J. Med., *263*:278-282, 1960.
53. Ratnoff, O. D., and Patek, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver. An analysis of 386 cases. Med., *21*:207-268, 1942.

54. Read, A. E., Sherlock, S., Laidlaw, J., Walker, J. G.: The neuro-psychiatric syndromes associated with chronic liver disease and an extensive portalsystemic collateral circulation. Quart. J. Med., *36*:135-150, 1967.
55. Richman, A., and Anthony, D.: Experiences with localized gastric hypothermia in massive upper gastrointestinal bleeding. Amer. J. Digest. Dis., 8:113-121, 1963.
56. Roberts, K. E., Vanamee, P., Poppell, J. W., Rubin, A., Braverman, W., and Randall, H. T.: Electrolyte alterations in liver disease and hepatic coma. MED. CLIN. N. AMER., *40*:901-914, 1956.
57. Rousselot, L. M., Gilbertson, F. E., and Panke, W. F.: Severe hemorrhage from esophagogastric varices: Its emergency management with particular reference to portacaval anastomosis. New Eng. J. Med., *262*:269-276, 1960.
58. Rousselot, L. M., Panke, W. F., Bono, F., and Moreno, A. H.: Experiences with portacaval anastomosis. Analysis of 104 elective end-to-side shunts for the prevention of recurrent hemorrhage from esophagogastric varices. Amer. J. Med., *34*:297-307, 1963.
59. Rousselot, L. M., Panke, W. F., and Moreno, A. H.: Further evaluation of splenic pulp pressure as a differential diagnostic test of acute upper gastrointestinal bleeding. Amer. J. Gastroenterol., *35*:474-478, 1961.
60. Sawyer, W. D., Fletcher, A. P., Alkyaersig, N., and Sherry, S.: Studies of the thrombolytic activity of human plasma. J. Clin. Invest., *39*:426-434, 1960.
61. Schwartz, S. I., Bales, H. W., Emerson, G. L., and Mahoney, E. B.: The use of intravenous pitressin in treatment of bleeding esophageal varices. Surg., *45*:72-80, 1959.
62. Sengstaken, R. W., and Blakemore, A. H.: Balloon tamponage for the control of hemorrhage from esophageal varices. Ann. Surg., *131*:781-789, 1950.
63. Shaldon, S., and Sherlock, S.: The use of vasopressin ('Pitressin') in the control of bleeding from oesophageal varices. Lancet, 2:222-225, 1960.
64. Shaldon, C., and Walker, R. M.: Emergency portacaval anastomosis. Lancet, 2:1003-1004, 1962.
65. Simpson, J. A., and Conn, H. O.: The role of ascites in gastroesophageal reflux. With comments on the pathogenesis of bleeding esophageal varices. Gastroenterology, *55*:17-25, 1968.
66. Spector, I., Corn, M., and Ticktin, H. E.: Effect of plasma transfusions on the prothrombin time and clotting factors in liver disease. New Eng. J. Med., *275*:1032-1037, 1966.
67. Stahl, J.: Studies of the blood ammonia in liver disease: The diagnostic, prognostic and therapeutic significance. Ann. Int. Med., *58*:1-24, 1963.
68. Summerskill, W. H. J., Davidson, C. S., Dible, J. H., Mallory, G. K., Sherlock, S., Turner, M. D., and Wolfe, S. J.: Cirrhosis of the liver. A study of alcoholic and non-alcoholic patients in Boston and London. New Eng. J. Med., *262*:1-9, 1960.
69. Taylor, F. W., and Jontz, J. G.: Cirrhosis with hemorrhage. Arch. Surg., *78*:786-790, 1959.
70. Verstraete, M., Vermylen, E., Vermylen, J., and Vandenbroucke, J.: Excessive consumption of blood coagulation components as cause of hemorrhage diathesis. Amer. J. Med., *38*:899-908, 1965.
71. Voorhees, A. B., Jr.: Management of portal hypertension. Bull. N.Y. Acad. Med., *35*:223-230, 1959.
72. Walker, G., Williams, R., Condon, R. E., Thompson, E. N., and Sherlock, S.: Gastric cooling in the treatment of bleeding from oesophageal varices. Lancet, 2:328-331, 1964.
73. Wangensteen, S. L., Orahood, R. C., Voorhees, A. B., Smith, R. B., III, and Healey, W. V.: Intragastric cooling in the management of hemorrhage from the upper gastrointestinal tract. Amer. J. Surg., *105*:401-412, 1963.
74. Wantz, G. E., and Payne, M. A.: The emergency portacaval shunt. Surg. Gynec. Obstet., *109*:549-554, 1959.
75. Wantz, G. E., and Payne, M. A.: Experience with portacaval shunt for portal hypertension. New Eng. J. Med., *265*:721-728, 1961.
76. Warren, W. D., Zeppa, R., and Fomon, J. J.: Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Arch. Surg., *166*:437-455, 1967.
77. Weinberger, H. A.: Emergency portacaval shunt for esophagogastric hemorrhage. Arch. Surg., *91*:333-337, 1965.
78. Young, P. C., Burnside, C. R., Knowles, H. C., and Schiff, L.: The effects of intragastric administration of whole blood on the concentration of blood ammonia in patients with liver disease. J. Lab. Clin. Med., *50*:11-16, 1957.

Veterans Administration Hospital
West Spring Street
West Haven, Connecticut 06516

The Management of Hepatic Coma

A Continuing Problem

THOMAS C. CHALMERS, M.D.*

It is appropriate to begin this discussion of the treatment of hepatic encephalopathy with two case histories, each fictitious but typical of many patients seen and treated by the author in their respective eras. Both had alcoholic cirrhosis of the liver and were admitted to a hospital with jaundice, ascites, and drowsiness. The first was treated in 1945 with a high-protein, high-calorie, high-vitamin diet. After 2 days in the hospital he was found to be too weak and tremorous to handle his knife and fork and he was fed by the house staff and nurses. The next day he was too comatose to swallow and a tube was passed, through which was fed a highly nutritious liquid diet containing 150 gm. of protein. His coma deepened in spite of what was considered to be the best possible therapy for his liver, and he died 2 days later.

The second patient was admitted 20 years later, in 1965, with a similar history and physical findings. Because of his obvious hepatic tremor he was placed on a zero-protein diet and oral neomycin. For 4 weeks in the hospital his mental symptoms fluctuated from semicoma to a mild tremor, but he was never considered alert enough to allow the protein in his diet to be raised to a minimal subsistance level. He died after steady deterioration of his liver function tests.

The sharply contrasting therapies prescribed for these two patients were considered highly appropriate by the superbly trained staff of the hospitals in which they died. The end came in spite of the best modern therapy. The severity of their illness was blamed for deaths that, in the light of changing knowledge, might well be called iatrogenic. One patient died of coma that was almost surely made worse by the high-protein diet prescribed for his liver. The second died of progressive liver disease that was surely not helped by the cirrhotogenic diet prescribed to protect his brain. Proper treatment for the second patient might still be obscure, but the first should certainly not have received a high-protein diet after signs of progressive encephalopathy appeared.

---

* Assistant Chief Medical Director for Research and Education, Veterans Administration, Washington, D.C. Formerly Professor of Medicine, Tufts University School of Medicine, and Chief of Medical Services, Lemuel Shattuck Hospital, Boston, Massachusetts.

Medical Clinics of North America—Vol. 52, No. 6, November, 1968

In the 1940-1950 decade, most patients with hepatic failure were treated with a high-protein diet.[9] Like most therapies employed before and since, this one was based on well-controlled but probably inappropriate animal experiments, and poorly controlled clinical trials. Since it is entirely likely that, through lack of essential knowledge, we are making the same serious mistakes at present in this and other fields, it is worthwhile listing the apparent reasons for our mistakes. The high-protein treatment of hepatic encephalopathy might have been avoided if we had been better acquainted with the medical literature, if more detailed data on the biochemical abnormalities responsible for cerebral changes in hepatic failure had been available, and if hypotheses about clinical management had been tested by well-controlled therapeutic trials. The state of our knowledge of hepatic encephalopathy in each of these areas will now be reviewed.

HISTORICAL OBSERVATIONS

In a review of hepatic coma published in 1948,[9] to which the author of this review contributed, the coma of Eck-fistula dogs fed high-meat rations was attributed to an encephalitis virus with great willingness because the information was incompatible with the observation that most patients did well on such a diet. Yet protein sensitivity was clearly demonstrated in Eck-fistula dogs in 1893 and attributed to ammonia in 1895.[4] Actually it was first described in a human in 1600. Summerskill[13] first pointed out in the medical literature that Sir Andrew Aguecheek of Shakespeare's *Twelfth Night* might well have had alcoholic cirrhosis and have described protein toxicity when he said, "Methinks sometimes I have no more wit than a Christian or an ordinary man has; but I am a great eater of beef, and, I believe, that does harm to my wit."

A number of papers were published in the first half of the twentieth century on protein and ammonia toxicity in patients with liver disease, and these will not be reviewed here. The modern era of extensive research on the mechanisms began with the observations of Gabuzda et al.[7] in 1952. Since that time it has been repeatedly documented that patients with liver disease and portacaval shunting of blood, especially the latter, may be exquisitively sensitive to dietary protein.

THERAPEUTIC APPLICATIONS. The therapeutic lesson to be learned from studies in which patients were their own controls is that withdrawal of protein and other nitrogen-containing substances is an effective, if occasionally transient, method of preventing and treating encephalopathy. The therapeutic enigma illustrated by the second patient is the advisability of such therapy in the cirrhotic who may already be severely protein-depleted. It is conceivable that the prescription of too little protein in the current effort to treat the brain is as bad for the patient as was the prescription of too much protein in the effort to treat the liver 20 years ago. In other words, adequate information of the kind that can be derived only from therapeutic trials is essential for proper conclusions about the place of dietary protein in the treatment of hepatic failure.

BIOCHEMICAL OBSERVATIONS

The second body of knowledge on which decisions about the treatment of hepatic encephalopathy are logically based is that concerned with biochemical mechanisms, largely the metabolism of ammonia. This reviewer is not competent to review the technical details, and a brief review is available.[15] However, it may be useful to cover briefly the evidence with regard to ammonia.

The Case for Ammonia Toxicity as a Cause of Hepatic Coma

Precipitation of encephalopathy by a variety of agents having as their common denominator the release of ammonia[10] is one of the best bits of evidence in favor of that substance as a major cause of mental symptoms in cirrhotics. Published data confirm that in patients not on antibiotics there is a significant correlation between the arterial ammonia level and depth of coma, but there is substantial overlap.[5] The clinically established hypersensitivity of patients with cirrhosis to gastrointestinal bleeding is well correlated with a singular rise in blood ammonia that is not seen in patients without cirrhosis.[3] Hypersensitivity to ingested or endogenous urea is probably the best evidence for a specific cause-and-effect relationship between ammonia and encephalopathy. It is hard to conceive how a substance as inert as urea could cause the train of symptoms encountered in cirrhosis unless it is by way of its well-documented breakdown into ammonia and carbon dioxide in the gastrointestinal tract.

Ammonia toxicity in animals is accompanied by coma, hyperventilation, and interference with Krebs cycle components in the blood and brain, but the differences between these experimental models and hepatic encephalopathy in man, especially the chronic form, are considerable.

Of crucial importance in understanding the biochemical aspects of ammonia toxicity are its apparent dependence upon pH gradients between extracellular and intracellular fluids. As a weakly ionized substance, the physical form of ammonia in biological fluids, a ratio of ammonia gas to ion (NH_3^0/NH_4^+) is pH-dependent. Since only the gas is freely diffusible across cell barriers, relative increases in extracellular pH (alkalosis) can result in significant relative increases of intracellular ammonium ion. Potassium deficiency and the acid-base changes that result from the administration of various diuretics are related to these changes in an intimate and deleterious manner. These principles have been well documented in the experimental animal,[14] but, as is so often the case, their application to prevention and therapy in man is far from clear.[8]

THERAPEUTIC APPLICATIONS. The therapeutic applications of the knowledge that ammonia is an important cause of hepatic coma are obvious. Its removal from the body should be facilitated, its production diminished, and, assuming only relative success in these two efforts, its effects on the brain should be neutralized. Removal of ammonia by the liver can be improved only by general measures to support liver function and by avoidance of surgical portacaval shunts except when they are necessary to prevent death from hemorrhage. Removal of urea and thereby ammonia by the kidney is facilitated by avoiding the prerenal azotemia that so frequently occurs in cirrhosis after dehydration, and by avoiding excessive use of paracenteses and diuretics. Artificial removal of ammonia by hemodialysis and peritoneal dialysis has had its advocates, but most clinicians are unimpressed by the results.

Production of ammonia can be diminished by efforts aimed at the two major organ sources, the gut and the kidney. Avoidance of excessive protein ingestion and administration of nonabsorbable antibiotics such as neomycin may be dramatically effective, especially the latter. However, the side effects of dogged therapy may be disastrous. The dangers of cirrhotogenic diets have been referred to. Neomycin is absorbed to a small degree and blood levels may rise to nephrotoxic levels in patients with renal failure. Production of ammonia by the colon can be diminished by removal of that organ or by diversion of the fecal stream from the colon, but both of these surgical maneuvers are major forms of therapy to be carried out in patients whose livers are functioning so poorly that they have chronic encephalopathy. Prevention of increased production by the kidney can be accomplished by correcting potassium deficiency and avoiding the excessive use of diuretics.

Protection of the brain against ammonia that is excessively produced or inadequately removed by the liver can be approached by three means that have evolved out of research into the science of ammonia metabolism. Arginine protects animals from lethal doses of amino acids and lowers the blood ammonia level in humans by increasing the net effect of the Krebs urea cycle. However, an intact liver is necessary, and the urea produced is in turn a toxic source of ammonia in the presence of renal failure. Glutamic acid also protects animals from ammonia toxicity, and the citric acid cycle and the transamination reactions by which it accomplishes this take place in the periphery as well as in the liver. However, it is highly insoluble except as sodium or potassium glutamate, and these salts, at least the former, may produce a deleterious alkalosis. Finally, the avoidance of electrolyte disturbances leading to alkalosis may diminish the toxicity of a given blood ammonia level.

The Case Against Ammonia Toxicity as the Sole Cause of Hepatic Coma

The lack of a complete correlation between blood ammonia levels and the state of consciousness has been referred to above. It is most striking in chronic encephalopathy treated by antibiotics[8] and in some cases of coma complicating acute hepatitis. The best example of the lack of correlation has occurred in a patient with fulminating hepatitis,[2] who was producing little or no urea and had a lower than normal blood ammonia level at the time of coma, decerebrate rigidity and convulsions, and a very high blood ammonia level after he had begun to make urea again and was wide awake. In this patient, as in many others, the apparent response to exchange transfusion in the state of consciousness suggests that some defect not involving toxic concentrations of ammonia was being corrected. It is unlikely that exchange could remove as much ammonia as dialysis, but it seems much more effective than the latter in lightening coma, although its influence on survival in fulminating hepatitis is still not established. It also seems probable that the occasional effects of other more drastic modes of coma therapy – cross perfusion with a normal volunteer or porcine liver perfusion – are more profound than mere removal of ammonia.

Finally of importance is the existence of other possible causes of hepatic coma, well reviewed by Zieve,[16] such as certain amino acid products and short-chain and medium-chain fatty acids. An abnormal shift in the hemoglobin dissociation curve[17] suggests a profound defect in oxygen metabolism that is not attributable to ammonia.

THERAPEUTIC APPLICATIONS. The therapeutic applications of the present knowledge about the "nonammonia" causes of hepatic coma are meager because that knowledge is so meager. However, it is apparent that most of the therapeutic benefit has already been derived from explorations of ammonia metabolism, and some new ideas are needed. When they do come along, it is fervently hoped that their application to patients will be tested in a more scientific manner than have past treatments of hepatic coma.

CLINICAL TRIALS OF HEPATIC COMA TREATMENTS

For every suggested therapy of hepatic coma there have been from 5 to 50 uncontrolled trials for every controlled one. In fact the latter are almost nonexistent. The efficacy and toxicity of dietary protein have never been tested in a trial employing randomization (the essential component of every well-controlled trial). Various antibiotics have been employed in a haphazard manner without any scientific information about their comparative efficacy. Paracentesis and diuretics have been variously interdicted as causes of coma when used to treat ascites, yet they have never been compared in an adequate trial. As each new therapy has been introduced, it has been assumed that it might be better than existing modalities, and a consecutive series of patients have been treated and compared with guesses about what the patients would have been like if not so treated, based on the vague experiences of the authors or reviews of the literature. The distorting effects of selection of patients in the case of the individual clinical investigator, and of papers in the case of the literature, are usually ignored.

Arginine[12] and sodium glutamate[1] have each been tried in single, moderately well controlled trials and found to be ineffective – hardly enough information to rule out their potential usefulness. Volume expansion during diuresis and paracentesis has been found in a controlled trial to be ineffective in preventing renal failure and coma.[6] Colon bypass[11] has been assessed in a controlled manner and been found to be mildly effective in reducing encephalopathy and to have no long-term effect on survival.

If there are any other controlled trials of the treatment of coma, this author does not know of them. This paucity of data results from several apparent characteristics of clinical investigators, all of which could be corrected:

1. Unwillingness of clinicians to recognize that a new therapy could be, on the average, more harmful than beneficial, and the resulting mistaken impression that it is more ethical to treat a selected series of patients than to randomize according to a carefully prepared protocol.

2. Unwillingness to begin randomization until the details of the new therapy have been worked out in a selected series of patients, by which time there is a strong inclination either to drop the treatment as ineffective or to continue without randomization because of the impression that it would be unethical to deprive future patients of an apparently promising therapy. Unless the expected outcome on conventional therapy is known with relative certainty, the first patient to receive a new treatment should be assigned at random to either conventional or experimental therapies. There are strong ethical as well as scientific arguments for this.

3. Unwillingness to undertake a controlled study because of fears about the numbers that would be required for definitive conclusions. These fears never stop clinical investigators from making judgments about the relative efficacy and toxicity of a new therapy tried in a small number of consecutively treated patients. It is a well-recognized truism that conclusions are easier to come by if controls are omitted.

4. Unwillingness to devote the time and effort required to set up and conduct a clinical trial, often requiring time-consuming cooperation among several clinics. To this there is no easy answer, except to emphasize that the rewards can be worth it. If each suggested therapy had been tested in a definitive manner from the beginning, we might not still be repeating the mistakes of the past, and we might now have more knowledge about how to treat hepatic coma. It seems probable that the lessons to be learned from our lack of complete success in the treatment of hepatic coma are applicable to most of the persisting therapeutic problems in medicine.

REFERENCES

1. Alexander, R. W., Berman, E., and Balfour, D. C., Jr.: Relationship of glutamic acid and blood ammonia to hepatic coma. Gastroenterology, 29:711, 1955.
2. Berger, R. L., Liversage, R. M., Jr., Chalmers, T. C., Graham, J. H., McGoldrick, D. M., and Stohlman, F., Jr.: Exchange transfusion in the treatment of fulminating hepatitis. New Eng. J. Med., 274:497, 1966.
3. Bessman, A. N., Mirick, G. S., and Hawkins, R.: Blood ammonia levels following ingestion of casein and whole blood. J. Clin. Invest., 37:990, 1958.
4. Chalmers, T. C.: An evaluation of dietary protein in the treatment of liver disease. Ann. Int. Med., 48:320, 1958.
5. Chalmers, T. C.: Pathogenesis and treatment of hepatic failure. New Eng. J. Med., 263:23, 1960.
6. Clermont, R. J., Vlahcevic, Z. R., Chalmers, T. C., Adham, N. F., Curtis, G. W., and Morrison, R. S.: Intravenous therapy of massive ascites in patients with cirrhosis. II. Long term effects on survival and frequency of renal failure. Gastroenterology, 53:220, 1967.
7. Gabuzda, G. J., Jr., Phillips, G. B., and Davidson, C. S.: Reversible toxic manifestations in patients with cirrhosis of the liver given cation-exchange resins. New Eng. J. Med., 246:124, 1952.
8. Moore, E. W., Strohmeyer, G. W., and Chalmers, T. C.: Distribution of ammonia across the blood-cerebrospinal fluid barrier in patients with hepatic failure. Amer. J. Med., 35:350, 1963.

9. Murphy, T. L., Chalmers, T. C., Eckhardt, R. D., and Davidson, C. S.: Hepatic coma. Clinical and laboratory observations on forty patients. New Eng. J. Med., 239:605, 1948.
10. Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S.: Syndrome of impending hepatic coma in patients with cirrhosis of liver given certain nitrogenous substances. New Eng. J. Med., 247:239, 1952.
11. Resnick, R. H., Ishihara, A., Chalmers, T. C., and Schimmel, E.: A controlled trial of colon by-pass in chronic hepatic encephalopathy. Gastroenterology, 54:1057, 1968.
12. Reynolds, T. B., Redeker, A. G., and Davis, P.: A controlled study of the effects of L-arginine on hepatic encephalopathy. Amer. J. Med., 25:359, 1958.
13. Summerskill, W. H. J.: Aguecheek's disease. Lancet, 2:288, 1955.
14. Warren, K. S.: The differential toxicity of ammonium salts. J. Clin. Invest., 37:1724, 1958.
15. Webster, L. T.: Hepatic coma—a biochemical disorder of the brain. Gastroenterology, 49:698, 1965.
16. Zieve, L.: Pathogenesis of hepatic coma. Arch. Intern. Med., *118*:211, 1966.
17. Zimmon, D. S.: Oxyhemoglobin dissociation in patients with hepatic encephalopathy. Gastroenterology, 52:647, 1967.

Veterans Administration Hospital
50 Irving Street, N.W.
Washington, D.C. 20422

Diagnostic Tests in Pancreatic Disease

DONALD H. HANSCOM, M.D.*

Few organs present greater obstacles to accurate diagnosis than the pancreas. It is the most inaccessible structure in the gastrointestinal system, since it cannot readily be palpated, visualized, opacified with radiopaque substances, or biopsied. Recognition of pancreatic disease is often based on metabolic effects, mechanical effects on other organs, demonstration of enzyme liberation, or clinical symptoms alone. Many diagnostic tests are available, but they must be selected with knowledge of the pathophysiology of the pancreas and the stage of the disease. It should be remembered that the pancreas has a large functional reserve, and evidence of impairment appears late.

ACUTE PANCREATITIS

This is usually a chemical inflammatory process resulting from the release of activated pancreatic enzymes into the parenchymal tissues. Both duct obstruction and stimulation of secretion are important factors in the initiation of inflammation. Pancreatic edema is the earliest response (acute edematous pancreatitis) and often subsides, but may progress to hemorrhage and necrosis (acute hemorrhagic pancreatitis). Alcoholism and biliary tract disease are the most common causes, but virus infections, trauma, metabolic diseases, and hereditary forms exist.

Clinical Findings

The clinical spectrum of acute pancreatitis is wide and ranges from mild episodes of tolerable abdominal pain to the severe pain and high mortality of hemorrhagic pancreatitis. Signs, symptoms, and useful diagnostic tests depend on the amount of inflammation present.

Acute pancreatitis is painful. Most patients complain of a *steady* epigastric pain which often bores into the back. Rarely it is felt only in the back, Some patients obtain partial relief by flexing the thighs on the trunk. Pancreatic pain is characteristically aggravated by eating—an important differential feature from acid-peptic disease. Vomiting and epigastric tenderness are usually present.

---

*Research Physician, Veterans Administration Hospital, Hines, Illinois; Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois

In edematous pancreatitis or mild inflammation associated with biliary tract disease or dysfunction of the sphincter of Oddi, there may be no finding other than pain. Unfortunately, many patients are labeled as neurotics because their symptoms are not properly considered and serum amylase or lipase determinations are not made. The following case is illustrative:

A 50-year-old nonalcoholic man had episodes of steady midepigastric pain lasting from 2 to 6 hours and radiating to the back. The pain usually began at 3 A.M., and relief occurred after meperidine injections. Epigastric tenderness and segmental hyperesthesia (see p. 1485) were the only findings. During several subsequent painful attacks, elevated levels of serum lipase and amylase and urinary amylase were present. Chronic cholecystitis and cholelithiasis were found at laparotomy and the pancreas was normal to palpation. He has had no more abdominal pain.

It would be difficult to prove that this patient's pain was not due to pancreatitis associated with biliary disease, since gross observations of the pancreas at laparotomy are often unreliable. Without better proof of pancreatic disease one might conclude that the enzymes were up in association with gallbladder disease. This example shows how limited we are in our diagnostic skills when minor degrees of inflammation may exist. A more definite case of edematous pancreatitis is the following:

A 33-year-old laborer drank a fifth of whiskey in an evening and came to the hospital the next day complaining of midepigastric pain and vomiting. Epigastric tenderness and cutaneous hyperesthesia were present. Serum and urine amylase and serum lipase levels were elevated, but returned to normal in 6 days. After 3 days of nasogastric suction, meperidine, intravenous fluids, and atropine, he became symptom-free and was placed on a bland diet and discharged on the tenth day. On the ninth day a secretin test showed low bicarbonate concentration and low volume output, but retesting after 3 months gave normal results.

Patients with alcoholism frequently come to the hospital with abdominal pain and vomiting, and we are too eager to diagnose gastritis as the cause of symptoms. It is doubtful if gastritis (whatever its cause) ever causes symptoms, and a consideration of pancreatitis is appropriate when managing such patients. In both cases presented, the diagnosis was reached by clinical awareness and detection of enzyme alterations during the acute phase. Measurements of exocrine (digestive) pancreatic function may give normal values, since the inflammation is self-limited and the gland often recovers completely.

Acute hemorrhagic pancreatitis is characterized by profound alterations of serum and urinary enzyme levels, shock, dehydration, and more intense pain. The diagnosis is often made if one suspects pancreatitis and obtains amylase and lipase measurements. A frequent problem is the differentiation from other catastrophic illnesses such as myocardial infarction, perforated viscus, and bowel obstruction. In these conditions pancreatic enzyme levels may be elevated, but are not as high as in pancreatitis, and some patients undergo diagnostic laparotomy. Clearly, more specific diagnostic tests are needed to resolve this problem.

In some patients with acute pancreatitis, bilateral zones of cutaneous hyperesthesia can be demonstrated in the fifth to ninth thoracic segments (Fig. 1). The autonomic efferents from the pancreas enter the

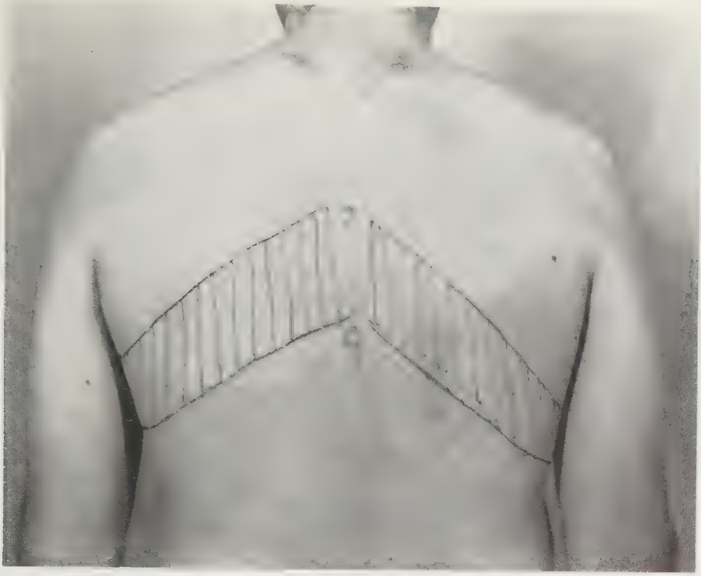

Figure 1. Zone of cutaneous hyperesthesia in a patient with acute pancreatitis.

spinal cord at this level and may stimulate local reflex pathways. Hyperesthesia of the skin is best elicited by light stroking down the back with a blunt instrument, but requires a responsive, cooperative patient. The hyperesthesia often extends anteriorly. While not pathognomonic of pancreatic disease, it is a finding which, when present, strongly suggests pancreatic-biliary disease, according to my experience.

Other clinical findings aiding in the diagnosis of pancreatitis although not unique to it are abdominal distention, paralytic ileus, subcutaneous ecchymoses in the flank (Grey-Turner sign) and umbilicus (Cullen's sign), pleural effusion, and obstructive jaundice.

Laboratory Tests

ENZYME ALTERATIONS. Estimation of serum lipase and amylase continues to be the easiest and most reliable test of acute pancreatitis. Regurgitation of these enzymes into the blood occurs when there is increased pressure in the pancreatic ducts and cellular disruption, although the degree of enzyme elevation is not necessarily related to the amount of gland destruction. Contrary to older concepts, the serum amylase and lipase usually rise and fall together. Recent studies with the colorimetric method of lipase determination suggest that lipase is more often elevated than amylase and may persist longer.[15] Improved techniques for differentiating pancreatic amylase from liver and salivary amylase will aid in diagnosis, but these methods are not generally available.[2] A 97 per cent accuracy in diagnosis of acute pancreatitis was achieved by Patt et al. when both serum amylase and lipase tests were performed.[15]

Urinary excretion of amylase may be increased when serum amylase is normal or only slightly elevated. Collection of a 24-hour urine specimen should begin as soon as the diagnosis is entertained. Pancreatitis may cause elevation of amylase levels in pleural or peritoneal fluid obtained by aspiration. Elevation of serum glutamic oxaloacetic transaminase (SGOT) occurs in some patients with acute pancreatitis, but it is unclear whether this results from pancreatic cell necrosis or extrahepatic biliary obstruction.[13]

METABOLIC ALTERATIONS. Hypocalcemia (occasionally causing tetany) may occur in hemorrhagic pancreatitis when serum calcium combines with fatty acids to form relatively insoluble soaps. The degree of serum calcium depression roughly parallels the severity of the pancreatitis. Hyperparathyroidism should be suspected when calcium levels are normal or elevated in severe pancreatitis. Hyperlipemia is occasionally seen in acute pancreatitis, but the mechanism is uncertain (see p. 1493). Temporary involvement of the islets of Langerhans may cause transient hyperglycemia and impaired glucose tolerance.

RADIOGRAPHIC FINDINGS. Adjacent organs may show alteration of form or function and this demonstration may aid in diagnosis. Adynamic ileus, pancreatic calcification, and an isolated gas-filled segment of small intestine (sentinel loop) are helpful radiographic signs. Barium meal examinations are best delayed, but later may show deformity of the duodenal loop from an enlarged pancreas or extrinsic pressure on the stomach or duodenum from a pancreatic cyst or an enlarged gallbladder. Occasionally the left diaphragm is elevated owing to basilar pneumonia or effusion. Oral cholecystography performed soon after recovery will usually result in nonvisualization of the gallbladder, but later may be normal. This fact is important in avoiding an incorrect diagnosis of gallbladder disease.

EXOCRINE TESTS. Analysis of pancreatic secretions after stimulation with secretin and pancreozymin may disclose impairment of exocrine function, but is of little value for diagnosis in the acute episode because of the large functional reserve of the pancreas. When tested 10 to 14 days after symptoms have subsided, some patients have abnormal results, particularly if the response to pancreozymin is included[9] (Fig. 2). Most patients show return to normal when retested after 3 months.

Conclusions

1. Early diagnosis of acute pancreatitis requires clinical suspicion. Less severe or atypical forms may escape recognition.
2. When the diagnosis is considered, estimation of serum lipase and amylase and urinary amylase should be done. Accuracy can be as high as 97 per cent.
3. Measurements of serum calcium, triglycerides, SGOT, and glucose may aid in diagnosis but are nonspecific.
4. Radiographic studies may demonstrate alteration of form or function of the pancreas or adjacent organs.
5. Testing exocrine function may reveal abnormalities, but because of the large functional reserve this is of little value in early diagnosis.
6. With atypical symptoms and equivocal laboratory tests we must consider every available piece of evidence – hence the need for a battery of laboratory tests.

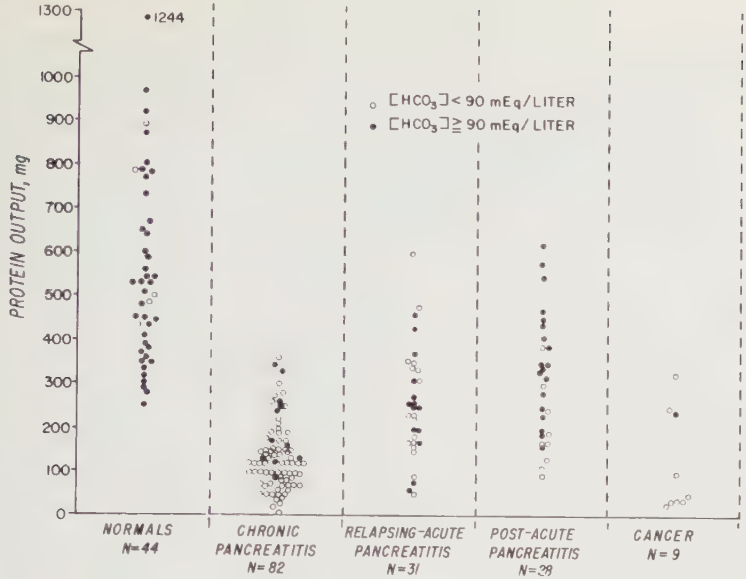

Figure 2. Protein output (mg.) after test dose of pancreozymin. Abnormal maximum bicarbonate concentrations in a preceding secretin test are indicated.

CHRONIC PANCREATITIS

Recurrent episodes of pancreatic inflammation commonly result in parenchymal fibrosis and duct obstruction with segmental dilation. The pancreatic duct may have a "chain-of-lakes" appearance with secretions under high pressure in the dilated segments. Eventually, pancreatic calcifications may develop.

Clinical Findings

The symptoms are the same as in acute pancreatitis, with intermittent episodes of painful inflammation (chronic relapsing pancreatitis). In some patients the pain is constant, but it is not uncommon for patients with chronic pancreatitis to be entirely free of pain and give no past history of painful episodes. Symptoms relating to the effects of exocrine or endocrine impairment may predominate. Steatorrhea is suspected when there is a history of loose, foul-smelling, foamy stools which float and may be difficult to flush. Weakness and weight loss are common and may be secondary to malnutrition or overt diabetes mellitus. As with acute pancreatitis, the diagnosis rests mainly on laboratory tests.

Laboratory Tests

ENZYME ALTERATIONS. Serum amylase and lipase may be elevated with painful relapses of chronic pancreatitis, but they rarely show striking elevations and are sometimes normal. Persistence of serum lipase and amylase elevations for more than 2 to 3 weeks after acute pancreatitis or a relapse of chronic pancreatitis is suggestive of complicating events such as pseudocyst or abscess formation. The provocative serum amylase and lipase response after administration of secretin and pancreozymin is occasionally helpful in diagnosis, but most patients with chronic pancreatitis do not have significant enzyme elevations when compared with baseline values. False positive responses do occur.

METABOLIC ALTERATIONS. Steatorrhea and diabetes occur so frequently in chronic pancreatitis and are of such great therapeutic importance that they should be sought whenever this diagnosis is considered. Documentation of steatorrhea requires quantitation of fecal fat excretion. A 72-hour stool collection is obtained and results are expressed as grams of fat per 24 hours, normal being less than 5 gm. When facilities for this analysis are not available, steatorrhea is likely present with strong sudan III fecal fat staining, or layering of fat in liquefied refrigerated stool specimens.

Finding impaired glucose tolerance in a patient with steatorrhea favors a pancreatic rather than an intestinal-absorptive etiology. In a group of 37 patients with chronic pancreatitis studied at Hines VA Hospital, oral glucose tolerance tests indicated diabetes or impaired carbohydrate tolerance in 30.[9] Many patients in our pancreatic clinic develop diabetes during follow-up and usually require insulin therapy.

The triolein test is designed to measure the hydrolysis of ^{131}I-labeled triolein by pancreatic lipase and the subsequent absorption of oleic acid. Low levels of serum radioactivity after triolein and normal levels after oleic acid are suggestive of lipase deficiency. This test has been criticized because of uncertainty of the compound's stability in the stomach and chemical or isotopic impurities. Abnormal tests are reliable only when there is gross steatorrhea. In our hands and in those of others it has not been a useful test and is occasionally misleading. Chey et al.[5] found abnormal triolein tests in only 36 per cent of patients with chronic pancreatitis and pancreatic cancer.

RADIOGRAPHIC FINDINGS. The findings may be similar to those in acute pancreatitis. Calcification is often present in the form of large irregular deposits in the ducts. Parenchymal calcification is less common and has the same significance.

Pancreatic scanning techniques are being devised which may aid significantly in diagnosis. A dual channel scanning system has been developed for recording the simultaneous distribution of two gamma-emitting radioisotopes.[3, 4, 7, 12] The pancreas and liver concentrate ^{75}selenomethionine, and colloidal radiogold is concentrated in the liver. The ^{75}Se activity is electronically subtracted from the liver and the distinctive peak of each isotope is analyzed and stored on magnetic tape. A time-exposure photograph of such a scan is shown in Figure 3. The isotopes can be printed out in different colors for greater clarity. This method has proved useful in the diagnosis of pancreatic disease.[7] A review of the dual channel scanning method and its application will appear in the January issue of the *Medical Clinics*.

EXOCRINE TESTS. *1. Secretin-Pancreozymin Test.* Analysis of the duodenal contents after stimulation with secretin and pancreozymin

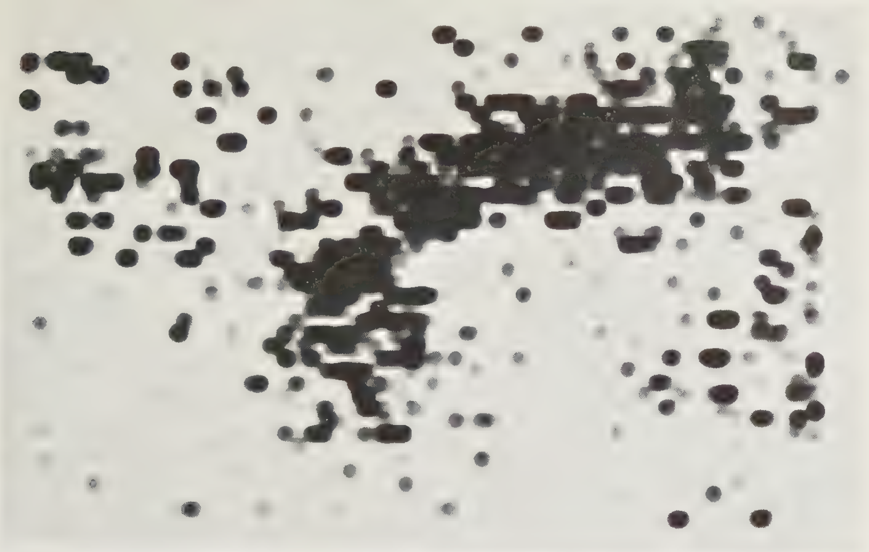

Figure 3. Pancreatic scan showing a normal pancreas. The liver activity has been subtracted. (From Kaplan, E., et al., J. Nuclear Med., 7:807, 1966.)

is the most sensitive and reliable test of pancreatic exocrine function. The secretin test has been available for several decades, but until recently secretin preparations were not well purified. Systemic reactions to foreign proteins in the preparation limited clinical investigations of the dose-response relationships. Recent purification techniques have yielded safer preparations. At present, Boots* secretin is the only commercially available preparation. Secretin has been synthesized in the laboratory, but is not yet commercially available.

The best standardized method of performing the secretin test is that of Dreiling and Janowitz.[6] They give 1.0 clinical unit of secretin per kilogram of body weight and collect duodenal juice for 80 minutes. The lower limits of normal in 1824 patients without pancreatic disease were: volume flow of 2.0 ml. per kg.; maximum bicarbonate concentration of 90 mEq. per liter; and amylase secretion of 6.0 u per kg. They feel that the most reliable measurement is maximum bicarbonate concentration. Secretin has also been given as a single "augmented" dose of 2.0 u per kg.[10] and as a constant intravenous infusion.[1]

Methods of pancreozymin usage have also varied. The hormone has been given with secretin and at varying time intervals before and after secretin. The amount of pancreozymin has varied from the contents of one ampule to 1 u per kg. to 4.5 u per kg. Based on dose-response studies in our laboratory, we use a dose of 4.5 u per kg. of pancreozymin, which appears to be the maximally tolerated amount.[8] We perform a 1-hour secretin test and then give a "flushing" dose of pancreozymin, followed in 30 minutes by the 4.5 u per kg. test dose.[9]

---

*Boots Pure Drug Co., Ltd., Nottingham, England.

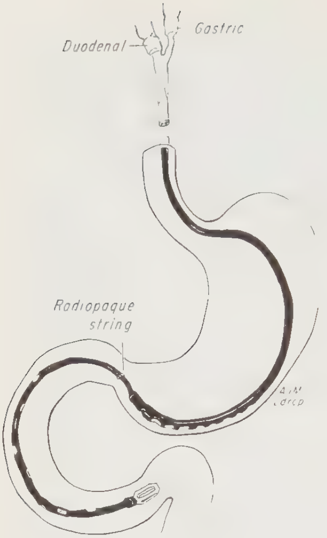

Figure 4. Position of double-lumen Dreiling tube for collection of duodenal juice.

Secretin-pancreozymin test procedure: A Dreiling double-lumen tube is passed into the duodenum under fluoroscopic control so that the metal olive is near the ligament of Treitz and a radiopaque marker at the distal end of the gastric tube is at the pylorus (Fig. 4). The duodenal contents are collected using a pump with 5 lb. negative pressure automatically interrupted for 5 seconds every minute. Gastric secretions are aspirated separately and discarded. If bile appears in the gastric collection, the tube is replaced with fluoroscopic aid.

Pancreozymin and secretin preparations are dissolved in isotonic saline to make a concentration of 10 u per ml. Intracutaneous tests are done with 1:10 dilutions of these solutions. If erythema or induration develop, the hormone preparation is not given.

A secretin test is performed by injecting 1.5 u per kg. of Boots secretin intravenously in 5 minutes and collecting six 10-minute specimens from the duodenal tube. The volumes are measured and bicarbonate and icteric index values estimated. At the end of the hour, a continuous intravenous infusion of secretin is begun at a rate of 1.5 u per kg. per hour in 180 ml. of saline solution using a Bowman pump. Simultaneously a "flushing" dose of pancreozymin, 1.5 u per kg., is injected intravenously and two 15-minute duodenal collections are obtained. Then 4.5 u per kg. of pancreozymin is given intravenously as the test dose, and two 15-minute collections are made, completing the test. The volumes are measured and the specimens are analyzed for bicarbonate, protein, amylase, trypsin, and icteric index.

The total protein output in the 15-minute specimen after the large dose of pancreozymin is believed to represent the best measure of response to pancreozymin. When this figure is plotted for normal controls and patients with pancreatic disease, and identified as being associated with a normal or abnormal maximal bicarbonate concentration with the secretin test, it is seen in Figure 2 that some patients would be regarded as normal if only secretin were used. Computer analysis of discriminant function suggests that pancreozymin is superior to secretin, but that using both hormones is better than either one alone.[9]

---

[*] GIH Research Unit, Chemistry Department, Karolinska Institutet, Stockholm, Sweden.

Other information can be obtained from analysis of duodenal juice. Cytologic study may be performed if cancer is suspected. The patient with the highest protein output in the cancer group in Figure 5 had malignant cells on cytologic examination, and laparotomy disclosed a carcinoma of the ampulla of Vater. If gallbladder disease is suspected, we perform microscopic examination of the bile to look for calcium bilirubinate and cholesterol crystals. The icteric index values are an accurate reflection of gallbladder function and common duct patency. When the gallbladder is functioning normally, at least one of the postsecretin specimens should be free of bile, indicating ability of the gallbladder to accept all the bile produced by secretin choleresis. Since pancreozymin preparations contain cholecystokinin, the first postpancreozymin specimen has a high icteric index value owing to evacuation of B-bile from the gallbladder. Absence of the gallbladder, obstruction of the cystic duct, or cholecystitis are characterized by constant bile staining after secretin, and complete obstruction of the common bile duct causes all specimens to be colorless.

Although performance of the test requires an experienced physician, fluoroscopic aid, and laboratory analyses, it could be done in most general hospitals. Secretin is available, but pancreozymin is still an investigational preparation. I know of no deaths attributed to the use of preparations presently available. Preliminary skin testing will detect sensitive patients who should not receive these preparations.

2. *Lundh Test.* The test measures the enzyme response of the pancreas to a test meal which causes release of endogenous secretin and pancreozymin.[14, 16]

A Rehfuss tube is positioned with fluoroscopic aid in the third portion of the duodenum. The test meal (126 gm. skim milk powder, 138 gm. dextrose, 74 gm. corn oil, 400 ml. tap water) is given, and six 10-minute aspirations and two 30-minute aspirations are obtained by hand suction. Aliquots of each specimen are pooled and a trypsin determination is made on the pooled specimen.

A low trypsin activity in the duodenal aspirate is good evidence that steatorrhea is of pancreatic origin. Test results are often normal in patients with mild or moderate pancreatic disease. We recommend using this test when one suspects chronic pancreatitis with exocrine insufficiency.

3. *Stool enzymes.* Measurements of fecal trypsin and chymotrypsin are of value in the diagnosis of pancreatic exocrine insufficiency, especially when specific enzyme substrates are utilized. Details of the test may be found in the article by Haverback et al.[11]

Conclusions

1. The diagnosis of chronic pancreatitis is largely based on laboratory tests.
2. Fasting or provocative serum enzymes are often normal.
3. Steatorrhea and impairment of glucose tolerance are frequent findings.
4. Pancreatic scanning shows great promise as an important diagnostic tool.

5. Analysis of duodenal drainage after stimulation with secretin and pancreozymin is the most reliable and sensitive measure of exocrine function. Icteric index values during the secretin-pancreozymin test are helpful in assessing gallbladder function.

6. The Lundh test meal is useful in detecting a pancreatic etiology of steatorrhea.

7. Far advanced chronic pancreatitis may be clinically evident, with laboratory tests needed only for confirmation.

REFERENCES

1. Banwell, J. G., Northam, B. E., and Cooke, W. T.: Secretory response of the human pancreas to continuous intravenous infusion of secretin. Gut, *8*:50, 1967.
2. Berk, J. E.: Serum amylase and lipase: Newer perspectives. J.A.M.A., *199*:98, 1967.
3. Ben-Porath, M., Clayton, G., and Kaplan, E.: Modification of a multi-isotope color scanner for multi-purpose scanning. J. Nucl. Med., *8*:411, 1967.
4. Ben-Porath, M., Clayton, G., and Kaplan, E.: The use of a tape recording device in simultaneous multi-isotope scanning. (In press)
5. Chey, W. Y., Shay, H., Nielsen, O. F., and Lorber, S. H.: Evaluation of tests of pancreatic function in chronic pancreatic disease. J.A.M.A., *201*:347, 1967.
6. Dreiling, D. A., and Janowitz, H. D.: The measurement of pancreatic secretory function. *In* de Reuck, A. V. S., and Cameron, M. P., eds.: Ciba Foundation Symposium on the Exocrine Pancreas. Boston, Little, Brown and Co., 1961, p. 225.
7. Fink, S., Ben-Porath, M., Jacobson, B., Clayton, G., and Kaplan, E.: Current status of dual channel pancreatic scanning. (In press)
8. Hanscom, D. H., and Littman, A.: Dose-response relationships to pancreozymin in normal subjects and patients with chronic pancreatitis. Gastroenterology, *45*:209, 1963.
9. Hanscom, D. H., Jacobson, B., and Littman, A.: The output of protein after pancreozymin: A test of pancreatic function. Ann. Int. Med., *66*:721, 1967.
10. Hartley, R. C., Gambill, E. E., Engstrom, G. W., and Summerskill, W. H. J.: Pancreatic exocrine function: Comparison of responses to augmented secretin stimulus, augmented pancreozymin stimulus, and test meal in health and disease. Amer. J. Digest. Dis., *11*:27, 1966.
11. Haverback, B. J., Dyce, B. J., Gutentag, P. J., and Montgomery, D. W.: Measurement of trypsin and chymotrypsin in stool. Gastroenterology, *44*:588, 1963.
12. Kaplan, E., Ben-Porath, M., Fink, S., Clayton, G., and Jacobson, B.: Elimination of liver interference from the selenomethionine pancreas scan. J. Nucl. Med., *7*:807, 1966.
13. Lukash, W. M., Bishop, R. P., and Nielsen, O. F.: Transaminase levels in acute pancreatitis and after secretin stimulation: Preliminary study. J.A.M.A., *197*:927, 1966.
14. Lundh, G.: Pancreatic exocrine function in neoplastic and inflammatory disease, a simple and reliable new test. Gastroenterology, *42*:275, 1962.
15. Patt, H. H., Kramer, S. P., Woel, G., Zeitung, D., and Seligman, A. M.: Serum lipase determination in acute pancreatitis. Arch. Surg., *92*:718, 1966.
16. Ventzke, L. E., Davidson, W. A., and Grossman, M. I.: Diagnostic value of pancreatic enzyme response to a test meal. Gastroenterology, *46*:765, 1964.

Veterans Administration Hospital
Hines, Illinois 60141

Relationship Between Acute Pancreatitis and Hyperlipemia

LESLIE ZIEVE, M.D.*

Much confusion surrounds the association of pancreatitis and lipemia. The prevailing impression is that lipemia is frequently due to pancreatitis. Yet in the nonalcoholic patient with acute pancreatitis, lipemia is rare. The two main reasons for the confusion are the association of pancreatitis with familial idiopathic hyperlipemia and with alcoholic fatty liver.

Pancreatitis occurs with increased frequency in patients with familial idiopathic hyperlipemia,[9] but in these patients the lipemia is antecedent to the pancreatitis. Such cases are infrequent. They form a separate entity that need cause no confusion if they are not grouped with cases of primary acute pancreatitis.

Most patients with acute pancreatitis seen in a general hospital are alcoholics who may also have fatty livers. The liver abnormality has been overlooked in the papers that have focused on the pancreatitis. There may or may not be an association between lipemia and the combination of fatty liver and pancreatitis; however, this has never been studied in a controlled fashion. Lipemia is known to be associated with fatty liver in the absence of clinically evident acute pancreatitis. However, no one has demonstrated that nonfamilial lipemia is associated with pancreatitis in the absence of a fatty liver. The work of Wang and Adlersberg[18, 19] is often cited in support of the latter association. These authors found a modest rise in serum cholesterol concentration in experimental and in human acute pancreatitis, but never provided control observations. Their experiments in dogs were repeated in our laboratory at the time of their report. The average preoperative and peak postoperative values observed with the serum amylase activity and total serum cholesterol concentration are shown in Figure 1. The increase in serum cholesterol concentration was significant ($t = 11.2$, $p < 0.01$) in the dogs with experimental pancreatitis, but was similarly significant in the sham-operated controls ($t = 10.5$, $p < 0.01$). Therefore a rise in serum

---

*Laboratory for Cancer Research and Department of Medicine, Minneapolis Veterans Hospital, University of Minnesota, Minneapolis

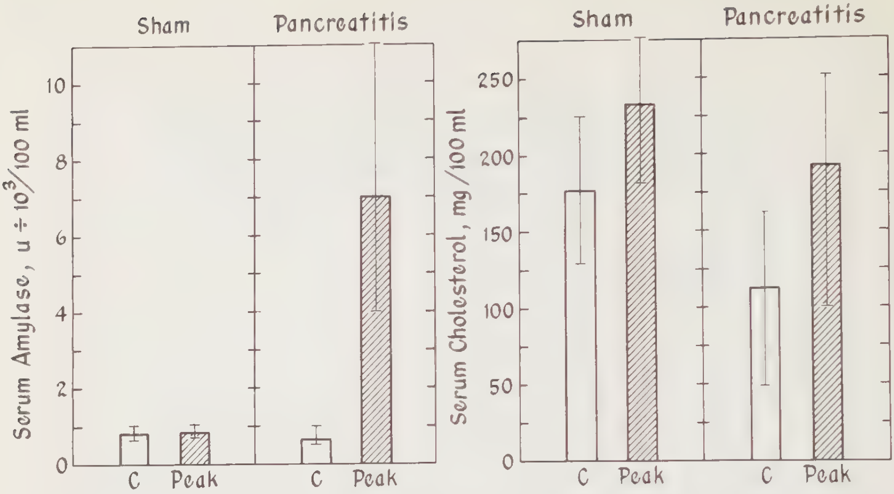

Figure 1. Serum amylase activity and cholesterol concentration in 4 sham-operated dogs and 7 with acute pancreatitis. The sham operation consisted of a resection of a piece of retroperitoneal fat through an abdominal approach. Acute pancreatitis was produced by injection of 2 to 3 ml. of the dog's gallbladder bile into the pancreatic duct under pressure. All animals received penicillin. *C*, preoperative control. *Peak*, highest postoperative value observed. The bars give the mean values and the vertical lines the *ranges* about the means, in this and all subsequent graphs.

cholesterol concentration cannot be cited as evidence for an effect of pancreatitis on serum lipids.

Albrink and Klatskin[1] reported on five lipemic patients with significant elevations in serum triglycerides (as well as other lipids), which they attributed to acute pancreatitis. Their patients all imbibed alcohol excessively and undoubtedly had fatty livers, though evidence bearing on this point was presented in only one case. The serum amylase activity was normal in the three patients who had serum drawn for the test. However "acute pancreatitis" was diagnosed at surgical exploration in one man, and a mass pressing on the stomach was observed on a gastrointestinal x-ray series in a second. Their paper presented various arguments for the pancreatic etiology of the lipemia, and has influenced the general thinking on this subject. However, factors of importance, such as malnutrition and alcoholism, were not taken into consideration in that report.

In 1966, Greenberger, Hatch, Drummey, and Isselbacher[1] reported on serum lipid alterations in 25 consecutive patients with acute pancreatitis, and found only three with lipemia. These three drank alcohol excessively, and undoubtedly had fatty livers, though this aspect of the patients was not discussed by the authors. Two were also diabetic. The serum amylase and lipase activities in these three patients were normal or minimally elevated, while their peak serum triglyceride concentrations were over 6000 mg. per 100 ml. (recorded only as milky serum in one of the cases). Their total serum cholesterol concentrations were over 800 mg. per 100 ml. The serum amylase and lipase activities of each of the other 22 patients were significantly elevated. Their highest average serum triglyceride concentration was 140 mg. per 100 ml. and total serum cholesterol concentration 216 mg. per 100 ml. Two of the three with lipemia were found to have edema and induration of the pancreas at exploratory laparotomy, and on this basis it was decided that they had had pancreatitis primarily. The authors suggested that in the three patients with lipemia there had been a latent defect in lipid metabolism associated with impaired ability to clear circulating glycerides, which was aggravated by the pancreatitis.

In the foregoing studies the variables of alcoholism and malnutrition with secondary fatty infiltration in the liver complicated the picture of acute pancreatitis in the patients who developed lipemia. What role, if any, the pancreatitis played in the etiology of the lipemia was impossible to judge, because there were no suitable controls. In order to evaluate the role of pancreatitis per se, we undertook some controlled studies in the dog.

STUDIES OF SERUM LIPIDS IN EXPERIMENTAL ACUTE PANCREATITIS

Procedures. The abdomen was entered in 15 normal dogs weighing approximately 40 to 50 pounds. In nine (seven male, two female), experimental pancreatitis was produced by injecting 8 to 10 ml. of a mixture of the dog's gallbladder bile (2 to 2.5 ml.) and olive oil (6 to 7.5 ml.) into the pancreatic duct. In six (three male, three female), a sham operation was performed and a piece of retroperitoneal fat resected. After completion of the operation each animal received daily therapeutic doses of penicillin. The two groups will be designated "sham" and "pancreatitis" dogs hereafter.

Two control studies, 2 to 3 days apart, were performed prior to surgery, and two test studies were performed on the first and fourteenth days after surgery. These two times were selected because our previous studies, during which serial samplings were made, had demonstrated that the peak serum enzyme elevation (amylase and lipase) occurred in approximately 24 hours, and then subsided progressively over a period of 2 weeks. After a fasting blood specimen was drawn for determination of serum triglyceride and cholesterol concentrations, each study consisted of the injection of 20 ml. of a lipid emulsion (Intralipid) and the sampling of blood for the measurement of serum triglyceride concentration at 15, 30, and 60 minutes. Serum triglyceride concentration was determined by the method of Van Handel and Zilversmit,[17] and serum cholesterol concentration by the method of Turner and Eales.[16]

Results. In Figure 2 are given values of the serum lipase activity before and after surgery. The sham-operated dogs showed no effects of surgery. After production of acute pancreatitis, the lipase activity rose 12-fold, but was back to control levels by the fourteenth day.

Fasting serum cholesterol concentrations rose similarly in both groups after operation (Fig. 3). The average percentage increase in the sham group was 35 per cent (range 13 to 97 per cent) and in the pancrea-

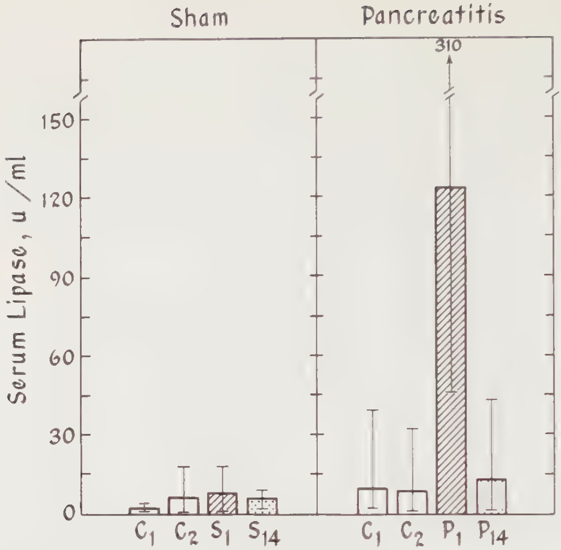

Figure 2. Serum lipase activity in 6 sham-operated dogs and 9 with experimentally-induced acute pancreatitis. In this and subsequent graphs, C_1 and C_2 are two preoperative control measurements. S_1 and S_{14} measurements on the first and fourteenth postoperative days in the sham-operated group, and P_1 and P_{14} the corresponding measurements in the dogs with pancreatitis. Lipase was determined by the method of Zieve and Vogel.[21]

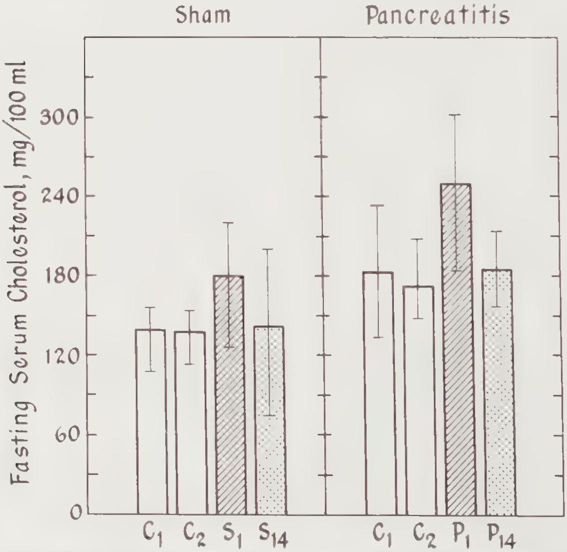

Figure 3. Fasting serum cholesterol concentrations in the sham and pancreatitis dogs. Tests of significance: Sham: C_1 vs. S_1, t = 3.54, $p < 0.02$. Pancreatitis: C_1 vs. P_1, t = 262, $p < 0.05$.

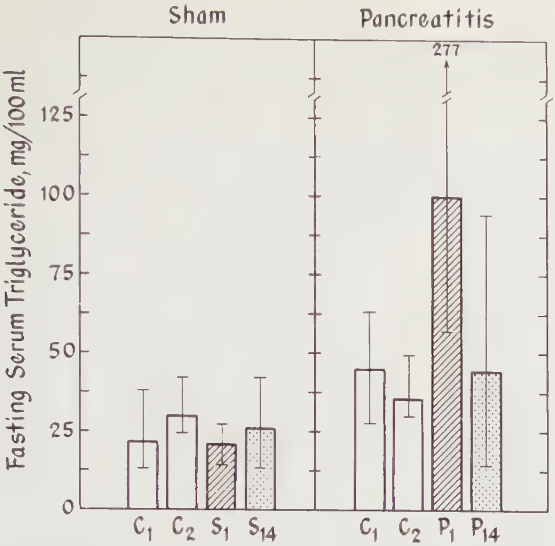

Figure 4. Fasting serum triglyceride concentrations in the sham and pancreatitis dogs. Test of significance: Pancreatitis: C_1 vs. P_1, $t = 2.65$, $p < 0.05$.

titis group 29 per cent (range 13 to 45 per cent). In contrast, the fasting serum triglyceride concentration rose significantly in the pancreatitis but not in the sham group (Fig. 4). In no instance however was the increase of the same order of magnitude as that seen in the patients with

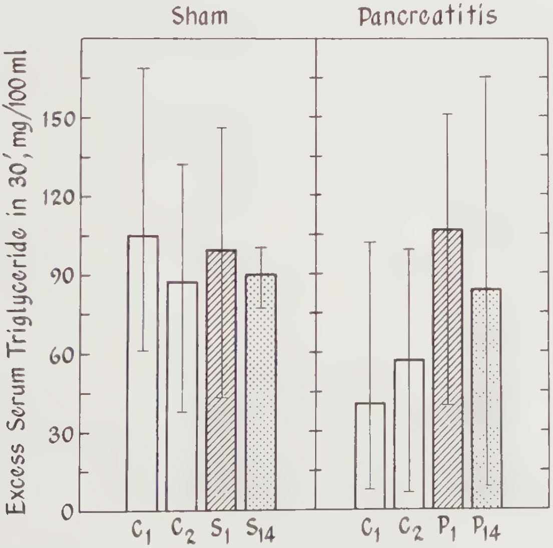

Figure 5. Excess serum triglyceride concentrations 30 minutes after an infusion of a fat emulsion in sham and pancreatitis dogs. "Excess triglyceride" is the difference between the measured value at 30 minutes and the preinfusion value. Test of significance: Pancreatitis: C_2 vs. P_1, $t = 3.36$, $p < 0.01$.

lipemia described by Albrink and Klatskin[1] or by Greenberger et al.[4] Within 2 weeks the average triglyceride value was back to control levels. Similar results were observed after the infusion of the fat emulsion. The excess triglyceride remaining in the serum 30 minutes after the infusion was approximately double (average increase of 184 per cent) the preoperative values in the pancreatitis group (Fig. 5), but unchanged from control levels in the sham group.

DISCUSSION

Bile-induced acute pancreatitis in the dog cannot be equated with alcohol-induced acute pancreatitis in man. However, the pathologic alterations in the pancreas are similar, so that one is perhaps justified in making comparisons regarding lipid abnormalities that have been thought to be associated with such pathologic alterations. It is evident that in the normal dog, under controlled conditions, pancreatitis does result in an increase in serum triglyceride concentration and an interference with the clearance of fat from the circulation. However the underlying abnormality does not result in a substantial rise in serum triglyceride concentration, such as that seen in the patients with lipemia. These data are consistent with the rarity of marked hypertriglyceridemia in acute pancreatitis occurring in nonalcoholic patients, and the infrequency of such hypertriglyceridemia in a sample of pancreatitis patients with a high incidence (at least 50 per cent) of alcoholism.[4] They suggest that pancreatic as compared to nonpancreatic factors play only a minor role, if any, in the etiology of the hyperlipemia observed in the patients reported by Zieve,[20] Albrink and Klatskin,[1] Losowsky et al.,[11] Greenberger et al.,[4] and many others.

Of the possible pancreas-related factors that might contribute to the development of lipidemia, two that deserve consideration at present are postheparin lipase and glucagon. Both of these substances enhance the breakdown and disposition of triglycerides. In the pancreatectomized or alloxan-treated animal, postheparin lipase activity is markedly reduced[12] and the clearance of infused fat delayed.[6] The abnormality is partially corrected by injections of insulin and completely corrected by the combination of insulin and the feeding of beef pancreas. Kessler and co-workers[7] reported the inhibition of normal rabbit plasma postheparin lipase activity by plasma from rabbits with staphylococcal toxin-induced acute pancreatitis. The pancreatitis had resulted in significant elevations of plasma triglycerides. Kessler et al.[8] also described a similar inhibition of normal plasma postheparin lipase activity in a patient with acute alcoholic pancreatitis associated with hyperlipemia. However, the same patient had later episodes of lipemia and enzyme inhibition associated with drinking in the absence of pancreatitis.

Losowsky and co-workers[11] have suggested that alcoholic hyperlipemia may be due, in part, to deficient removal of triglycerides from the blood by extrahepatic tissues because of reduced postheparin lipase activity. They observed low values for this enzyme in their patients who were lipemic. However their tables reveal low values for this enzyme in some of the patients when they were not lipemic and vice versa, so that this seems an unlikely etiologic factor. Examples that they observed of the lack of correlation between plasma lipoprotein lipase activity and lipid concentration are shown in Table 1.

Glucagon also enhances the clearing of lipid from the circulation, and lipidemia occurs under conditions in which there is a deficiency of glucagon, as in (1) depancreatized animals receiving injections of insulin along with crude pancreas in their diet as a source of enzymes,[3] (2) dogs with incomplete pancreatectomy involving the alpha cell-containing body and tail,[13] and (3) animals injected with cobalt chloride, which selectively destroys the alpha cells of the islets.[2] However, pancreatitis is not such a state of glucagon deficiency, being rather a state of glucagon excess.[14]

The nonpancreatic factors of prime importance in the etiology of the lipemia occurring in the kinds of patients being considered are excessive alcohol ingestion and hepatic injury. Among the most important effects of alcohol are (1) an increase in the mobilization of fatty acids with movement from fat depots to the liver, (2) an increase in the incorporation of fatty acids into triglycerides with an increased net production of liver triglycerides, and (3) a decrease in the formation of lipoproteins by the liver with a progressive decrease in the release of triglycerides.[5] There is probably a genetic basis for the susceptibility to this effect of alcohol, which may account for the variable nature of the responses to alcohol seen among alcoholics. As the liver cell injury proceeds, the interference with protein formation probably becomes increasingly important in the accumulation of neutral fat in the liver.

The production of lipemia in response to alcohol is probably biphasic. Early in the course of excessive alcohol ingestion, there is a modest elevation of plasma triglycerides because (1) the flux of fatty acids from fat depots to liver increases, (2) the incorporation of fatty acids into liver triglycerides increases, and (3) the supply of lipoproteins is adequate for transport of the triglycerides from the liver to the circulation. As the liver

Table 1. *Examples of Lack of Correlation Between Plasma Lipoprotein Lipase Activity and Lipid Concentrations**

PATIENT AND TIME AFTER ADMISSION	LIPOPROTEIN LIPASE (μEq. FFA/ml./min.)	PLASMA TRIGLYCERIDE (mg./100 ml.)
Pt. 1, 7 days	0.163	825
5 months	0.162	121
Pt. 2, Adm. 1, 1 day	0.129	2122
Adm. 2, 15 months	0.116	278
Pt. 3, 6 days	0.242	9400
Pt. 5, 123 days	0.256	77
Pt. 6, 1 day	0.161	748
Pt. 7, 1 day	0.243	740
Mean of 7 normals	0.277	–
Range of 7 normals	0.206–0.360	–

*Data of Losowsky et al.[11]

cell becomes injured, lipoprotein formation decreases and the accumulating triglycerides cannot be released as readily from the liver. The liver enlarges with fat, while the movement of triglycerides to the circulation probably decreases and the lipemia subsides. Once the drinking stops, the reparative process proceeds rapidly in the liver with the formation of lipoproteins and the rapid mobilization and outpouring of triglycerides into the circulation. The recrudescent lipemia in this phase may be marked, but is comparatively transient. It diminishes when the liver is emptied of its excess triglyceride, and the excessive diversion of fatty acids to triglycerides ceases. The evidence for this biphasic pattern is circumstantial, since no controlled study of such patients from beginning to end of their drinking and illness are available. However the first phase is suggested by the studies of Lieber et al.[10] and Shapiro et al.,[15] and the second phase is suggested by our observations[20] of the association of the rise and fall of serum lipids with the shrinking of the liver as the patient improves after hospitalization.

SUMMARY

Experimental acute pancreatitis in the dog results in a slight abnormality of the concentration of serum triglycerides and the clearance of infused fat. The basis for the confusion presently existing regarding the association of lipemia and acute pancreatitis has been reviewed, and evidence from the literature has been presented to indicate that alcoholism resulting in hepatic injury is the usual reason for the hyperlipemia that is seen in patients with acute pancreatitis, rather than the pancreatitis per se.

ACKNOWLEDGMENTS

I am grateful to Eugene Furry and Ann McHale for expert assistance, and to Dr. George Cronheim and Riker Laboratories for providing the fat emulsion.

REFERENCES

1. Albrink, M. J., and Klatskin, G.: Lactescence of serum following episodes of acute alcoholism and its probable relationship to acute pancreatitis. Amer. J. Med., *23*:26, 1957.
2. Caren, R., and Carbo, L.: Pancreatic alpha-cell function in relation to cholesterol metabolism. J. Clin. Endocrinol., *16*:507, 1956.
3. Dragstedt, L. R., Clarke, J. S., Hlavacek, G. R., and Harper, P. V., Jr.: Relation of the pancreas to the regulation of the blood lipids. Amer. J. Physiol, *179*:439, 1954.
4. Greenberger, N. J., Hatch, F. T., Drummey, G. D., and Isselbacher, K. J.: Pancreatitis and hyperlipemia: A study of serum lipid alterations in 25 patients with acute pancreatitis. Medicine, *45*:161, 1966.
5. Isselbacher, K. J., and Greenberger, N. J.: Metabolic effects of alcohol on the liver. New Eng. J. Med., *270*:351, 402, 1964.
6. Kessler, J. I.: Effect of insulin on release of plasma lipolytic activity and clearing of emulsified fat intravenously administered to pancreatectomized and alloxanized dogs. J. Lab. Clin. Med., *60*:747, 1962.
7. Kessler, J. I., Finkel, M., Ho, P-P., and Janowitz, H. D.: Lipoprotein lipase inhibition in rabbits with experimental pancreatitis. Proc. Soc. Exp. Biol. Med., *110*:24, 1962.
8. Kessler, J. I., Kniffen, J. C., and Janowitz, H. D.: Lipoprotein lipase inhibition in the hyperlipemia of acute alcoholic pancreatitis. New Eng. J. Med., *269*:943, 1963.

9. Klatskin, G., and Gordon, M.: Relationship between relapsing pancreatitis and essential hyperlipemia. Amer. J. Med., *12*:3, 1952.
10. Lieber, C. S., Jones, D. P., and Mendelson, J. H.: Fatty liver, hyperlipemia and hyperuricemia produced by prolonged alcohol consumption despite adequate dietary intake. Trans. Assoc. Amer. Physicians, 76:289, 1963.
11. Losowsky, M. S., Jones, D. P., Davidson, C. S., and Lieber, C. S.: Studies of alcoholic hyperlipemia and its mechanism. Amer. J. Med., *35*:794, 1963.
12. Meng, H. C., and Goldfarb, J. L.: Heparin-induced lipemia clearing factor in rats. Role of the pancreas in its production. Diabetes, *8*:211, 1959.
13. Paloyan, E., and Harper, P. V., Jr.: Glucagon as a regulating factor of plasma lipids. Metabolism, *10*:315, 1961.
14. Paloyan, E., Paloyan, D., and Harper, P. V., Jr.: The role of glucagon hypersecretion in the relationship of pancreatitis and hyperparathyroidism. Surgery, 62:167, 1967.
15. Shapiro, R. H., Drummey, G. D., Scheig, R., Mendelson, J. H., and Isselbacher, K. J.: Abnormalities of lipid transport accompanying prolonged alcohol ingestion in man. Gastroenterology, *44*:849, 1963.
16. Turner, T. J., and Eales, L.: Quantitative determination of cholesterol in serum with p-toluene-sulphonic acid. Scand. J. Clin. Lab. Invest., *9*:210, 1957.
17. Van Handel, E., and Zilversmit, D. B.: Micromethod for the direct determination of serum triglycerides. J. Lab. Clin. Med., *50*:152, 1957.
18. Wang, C., Adlersberg, D., and Feldman, E. B.: Serum lipids in acute pancreatitis. Gastroenterology, *36*:832, 1959.
19. Wang, C., Strauss, L., and Adlersberg, D.: Experimental pancreatitis and plasma lipids. Gastroenterology, *35*:465, 1958.
20. Zieve, L.: Jaundice, hyperlipemia and hemolytic anemia. A heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. Ann. Int. Med., *48*:471, 1958.
21. Zieve, L., and Vogel, W. C.: Measurement of lecithinase A in serum and other body fluids. J. Lab. Clin. Med., *57*:586, 1961.

Minneapolis Veterans Hospital
Minneapolis, Minnesota 55417

Statement of Ownership, Management, and Circulation
(Act of October 23, 1962; Section 4369, Title 39, United States Code)

1. Date of filing: September 15, 1968.
2. Title of publication: The Medical Clinics of North America.
3. Frequency of issue: Six times annually.
4. Location of known office of publication: 580 Hampton Road, Cherry Hill Township, New Jersey 08034.
5. Location of the headquarters or general business offices of the publisher: West Washington Square, Philadelphia, Pa. 19105.
6. Names and addresses of publisher, editor, and managing editor: Publisher, W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105; Editor, Albert E. Meier, c/o W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105; Managing Editor, none.
7. Owners: A. Paul Burton, John L. Dusseau, Harry R. Most, Sherman E. Perkins, Lawrence Saunders, W. Grier Saunders, and T. VandenBeemt, each of W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105; Sally L. Craigie, Martha S. Ferguson, Frances P. Kellogg, Margaret P. Manlove, Emily S. Perkins, Dorothy L. Saunders, Morton T. Saunders, and Nancy Gayle Whittingham, each of Bryn Mawr, Pa.; Charles C. Perkins, Jr., Atlanta, Ga.; and Anna B. Holmes, Corning, N.Y.
8. Known bondholders, mortgagees, and other security holders owning or holding 1 per cent or more of total amount of bonds, mortgages, or other securities: None.
9. Paragraphs 7 and 8 include, in cases in which the stockholder or security holder appears upon the books of the company as a trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting. Also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages, or other securities of the publishing corporation have been included in paragraphs 7 and 8 when the interests of such individuals are equivalent to 1 per cent or more of the total amount of the stock or securities of the publishing corporation.

10.

	Av. No. Copies Each Issue During Preceding 12 Mos.	Single Issue Nearest to Filing Date
A. Total number of copies printed (net press run)	42,600	42,500
B. Paid circulation		
1. Sales through dealers and carriers, street vendors, and counter sales	24,600	24,600
2. Mail subscriptions	13,200	13,100
C. Total paid circulation	37,800	37,700
D. Free distribution (including samples) by mail, carrier, or other means	300	300
E. Total distribution (sum of C and D)	38,100	38,000
F. Office use, left-over, unaccounted, spoiled after printing	4,500	4,500
G. Total (sum of E and F—should equal net press run shown in A)	42,600	42,500

I certify that the statements made by me above are correct and complete.

T. VandenBeemt, Vice President and Treasurer

Index for Years 1966, 1967, and 1968

(Volumes 50, 51, and 52)

Note: The volume year is in *italic* type. Page numbers of symposium and article titles are in **boldface** type.

SYMPOSIA

1966

January (Chicago)	Conquering Heart Disease
March (Lahey Clinic)	Systemic Disease and the Gastrointestinal Tract
May (Memorial Sloan-Kettering Cancer Center)	Recent Advances in Cancer
July (Mayo Clinic)	Diseases of the Kidney
September (Philadelphia)	Recent Advances in Medicine
November (Nationwide)	Hematologic Disorders

1967

January (Chicago)	Vascular Diseases
March (Nationwide)	Modern Management of Respiratory Diseases
May (Jefferson Medical College–Pennsylvania State University)	Infectious Diseases: Prevention and Immunization
July (Ochsner Clinic)	Unusual Clinical and Laboratory Manifestations of Disease
September (Nationwide)	Efficacy of New Drugs
November (Nationwide)	Psychiatry for the Nonpsychiatrist

1968

January (Chicago)	Pain and Its Clinical Management
March (St. Louis)	Endocrine Disorders
May (International)	Rheumatoid Arthritis
July (Mayo Clinic)	Neurologic Disorders
September (Nationwide)	Recent Advances in Cardiovascular Disease
November (Veterans Administration Hospitals)	Gastrointestinal and Liver Disease

Abdomen, masses in, differential diagnosis by lymphangiography, *1967*: Jan., 243
  in hypernephroma, *1966*: July, 1074
  pain in, diagnosis, *1966*: March, **439-447**
  patterns of, *1968*: Jan., 104-108
Abdominalgia, periodic, *1966*: March, 373
Abnormalities and deformities, low back pain and, *1968*: Jan., 58
Abruptio placentae, fibrinolysis in, with bleeding, *1967*: July, 1065, 1068
Abscess, bronchial, *1967*: March, 536
  in cancer surgical wound, treatment, *1966*: May, 794
  kidney, arteriogram in, *1967*: Jan., 61, 64, 65

- Abscess (*Continued*)
  - lung. See *Lung, abscess.*
  - parenchymal, acute, *1967*: March, 529
- Absorption, mechanisms of, localization, *1968*: Nov., 1344
  - normal, *1968*: Nov., 1340-1345
- Absorptive disorders. See *Malabsorption.*
- Acanthosis nigricans in carcinoma of lung, *1967*: July, 1043
  - malignant, *1966*: March, 358
- Accidental death in aged persons, *1967*: Nov., 1519
- Acetaminophen, site of action, *1968*: Jan., 8
- Acetazolamide (Diamox), for refractory heart failure, *1968*: Sept., 1173
- Acetylcysteine, as aerosol, *1967*: March, 312
  - for chronic bronchitis, *1967*: Sept., 1172
- Acetylsalicylic acid, for rheumatism, *1967*: Sept., 1213
  - site of action, *1968*: Jan., 8
- Achylia, pancreatic, in mucoviscidosis, *1966*: March, 452
- Acid-base, changes, in nonmetabolic disturbances of alveolar ventilation, *1967*: March, 408
  - disturbances, in cancer, *1966*: May, 714
  - metabolism, *1966*: May, 712
  - regulation, clinical disorders of, practical aids to diagnosis, *1966*: Sept., 1347
    - survey of 17 years' diagnostic experience, *1966*: Sept., **1325-1350**
- Acidosis, metabolic, *1966*: Sept., 1332
    - in cancer, *1966*: May, 717
    - plus metabolic alkalosis, *1966*: Sept., 1343
      - and respiratory alkalosis or acidosis, *1966*: Sept., 1344
    - plus respiratory acidosis, *1966*: Sept., 1341
  - respiratory, *1966*: Sept., 1337
    - diagnosis and management, *1967*: March, **293-305**
    - etiology, *1967*: March, 296
    - in cancer, *1966*: May, 714
    - in status asthmaticus, treatment, *1967*: March, 383, 384
    - plus metabolic acidosis, *1966*: Sept., 1341
    - plus metabolic alkalosis, *1966*: Sept., 1343
    - use of buffers in, *1967*: March, 329
  - uremic, in renal failure, *1966*: July, 1181
- Acneiform eruptions, drug, *1967*: July, 1076, 1083
- Acridine orange, fluorescent microscopy with, in gastric cytology, *1966*: May, 755
- Acrisorcin, topical, for fungus infections, *1967*: Sept., 1182
- Acromegaly, laboratory tests in, *1968*: March, 371
- Acromioclavicular joint, in rheumatoid arthritis, *1968*: May, 497
- Acropachy, in Graves' disease, *1967*: July, 920
- Acropathy, mutilating, *1968*: July, 899
  - thyroid, *1968*: March, **393-398**
- ACTH, production, in nonendocrine cancer, *1966*: May, 770
  - vs. corticosteroids in encephalitis, *1967*: Sept., 1197
- Actinomycetes, thermophilic, as source of farmer's lung, *1967*: March, 473
- Actinomycin D as anticancer agent, *1966*: May, 860, 866
- Actinomycosis, pulmonary, *1967*: March, **519-527**
- Activity. See *Exercise.*
- Addiction, to drugs, *1968*: Jan., 34
- Addison's disease, *1968*: March, **327-338**
  - diabetes mellitus and, *1968*: March, 336
  - erythropoiesis in, *1968*: March, 238
  - hyperthyroidism and, *1968*: March, 335
  - hypothyroidism and, *1968*: March, 334
- Adenohypophysis, hormones of, regulation of secretion, *1968*: March, 357
- Adenoma(s), chromophobe, endocrine glands and, *1968*: July, 830-834
    - symptoms and signs of, early, *1968*: July, **827-834**
  - endocrine, multiple, *1967*: July, 871, 874
    - peptic ulcer and, *1968*: Nov., 1278
  - islet cell, tolbutamide and leucine tolerance tests in, *1968*: March, 287
- Adenosine diphosphate in hemostasis, *1966*: Sept., 1266
- Adenovirus, infections, in adults, *1967*: May, 812
    - in children, *1967*: May, 822, 827
  - respiratory disease and, *1967*: May, **769-779**
  - vaccines, *1967*: May, 773, 776
- Adenylcyclase, adrenergic receptors and, *1968*: Sept., 1014
- ADH. See *Hormone, antidiuretic.*
- Adie's pupil, *1968*: July, 880
- Adolescents, catastrophic reactions in, *1967*: Nov., 1442
  - fears in, *1967*: Nov., 1450
  - home and parents, *1967*: Nov., 1440
  - mental illness in, diagnosis, *1967*: Nov., 1447
  - panic states in, *1967*: Nov., 1445
  - personality disorders in, *1967*: Nov., 1449
  - psychiatric emergencies in, *1967*: Nov., 1445

Adolescents (*Continued*)
psychopathic behavior in, *1967*: Nov., 1449
with school difficulties, *1967*: Nov., 1441
working with, some considerations in, *1967*: Nov., **1439-1451**
Adrenal cortex, hormones, influence on renal function, *1966*: July, 988
Adrenal glands, adenoma, aldosterone-producing, hypertension due to, *1966*: Jan., 294
atrophy, idiopathic, *1968*: March, 330
chromophobe adenoma and, *1968*: July, 831
disorders, amenorrhea and, *1968*: March, 344
function, erythropoiesis and, *1968*: March, 237
in amenorrhea, *1968*: March, 351
leukopoiesis and, *1968*: March, 240
fungus infections, *1968*: March, 328
hyperplasia, clinical and pathological characteristics, *1968*: March, 317
treatment for, *1968*: Sept., 1228
infections, *1968*: March, 327-330
insufficiency, orthostatic hypotension and, *1968*: July, 812
tuberculosis, *1968*: March, 327
tumors, amenorrhea and, *1968*: March, 344
clinical and pathological characteristics, *1968*: March, 317
diagnosis, *1968*: Sept., 1217
metastatic, *1968*: March, 330
pathophysiology, *1968*: March, 320
treatment, *1968*: March, 324
Adrenalectomy for carcinoma of breast, *1966*: Sept., 1463
Adrenalin. See *Epinephrine*.
Adrenergic blocking agents in hypertension, *1967*: July, 991
Adrenergic receptors, blockers of, *1968*: Sept., 1011
angina pectoris and, *1968*: Sept., **1031-1039**
cardiac arrhythmias and, *1968*: Sept., **1017-1029**
hyperdynamic cardiovascular states and, *1968*: Sept., **1041-1048**
in shock, *1968*: Sept., **1049-1060**
mechanism of action, *1968*: Sept., 1017-1019, 1052
sympathetic nervous system and, *1968*: Sept., **1049-1060**
concepts of, *1968*: Sept., **1009-1016**
in blood vessels, *1968*: Sept., 1012, 1079
subgroups, *1968*: Sept., 1013
Adrenocortical diseases, hyperfunctioning, etiology and diagnosis, *1967*: July, **883-901**
Adrenocortical insufficiency, chronic. See *Addison's disease*.
Adrenocorticoids. See *Corticosteroids*.
Adrenocorticotropin. See *ACTH*.
Adrenogenital syndrome, amenorrhea and, *1968*: March, 344
etiology and diagnosis, *1967*: July, **883-901**
Aerosol therapy, *1967*: March, 307-315
Aerosols, agents used as, *1967*: March, 310-315
Age, influence on enteric infections, *1967*: May, 643
Aged persons, mental disorders in, psychotherapy, *1967*: Nov., 1522
test to evaluate, *1967*: Nov., 1521
psychologic and emotional disorders in, management, *1967*: Nov., **1515-1527**
splenectomy in, *1966*: Nov., **1533-1558**
state hospitals and, *1967*: Nov., 1473
Agglutinins, cold, role, in blood incompatibility, *1966*: Nov., 1645
Agranulocytosis, oral lesions, *1966*: March, 368
Agrypnotic drugs, anorexia from, *1968*: July, 785-786
use of, general considerations, *1968*: July, 781
pitfalls in, *1968*: July, 784-785
Air embolism and its treatment, *1967*: *Sept.*, 1306, 1308
Akrinol, *1967*: Sept., 1182
Alcohol, as aerosol, *1967*: March, 315
as neurolytic agent, *1968*: Jan., 163
excessive intake, polyneuropathy and, *1968*: Jan., 112
heart disease and, *1968*: Sept., **1183-1191**
liver disease and, implications of current research in, *1968*: Nov., 1404
Alcoholism, cirrhosis and, *1968*: Nov., **1445-1455**
drug therapy, *1967*: Sept., **1249-1259**
Aldactone. See *Spironolactone*.
Alderlin. See *Pronethalol*.
Aldomet. See *Methyldopa*.
Aldosterone, in production of hypertension, *1967*: Jan., 4, July, 861, 973
influence on renal function, *1966*: July, 988
secretion, angiotensin and, *1968*: March, 267
practical test for, *1967*: July, 864
Aldosterone antagonists, for refractory heart failure, *1968*: Sept., 1174
Aldosteronism, primary, diagnosis, *1968*: 1223
hypertension due to, *1966*: Jan., 294
treatment, *1968*: Sept., 1228

- Aldosteronism (*Continued*)
  - primary, unusual manifestations and a practical approach to diagnosis, *1967:* July, **861-870**
- Algesic agents, chemical, *1968*: Jan., 4-6
- Alkaline phosphatase, plasma, hyperparathyroidism and, *1968*: March, 454
  - serum, test for, *1968*: Nov., 1410, 1428, 1429
- Alkalosis, metabolic, *1966*: Sept., 1335
    - in cancer, *1966*: May, 717
    - in ventilating patients with respiratory acidosis, *1966*: Sept., 1346
    - plus metabolic acidosis, *1966*: Sept., 1343
    - plus respiratory acidosis, *1966*: Sept., 1343
    - plus respiratory alkalosis, *1966*: Sept., 1341, 1342
  - potassium therapy for, *1968*: Sept., 1105
  - respiratory, *1966*: Sept., 1336
    - following alkali therapy of metabolic acidosis, *1966*: Sept., 1345
    - in cancer, *1966*: May, 714
    - plus metabolic acidosis, *1966*: Sept., 1341, 1342
  - subtraction, disorders of renal function with, *1966*: July, 1001
  - systemic, drugs causing, *1966*: March, 570
- Alkylating agents, for Hodgkin's disease, *1966*: Nov., 1606
  - for multiple myeloma, *1966*: Nov., 1570, 1573
  - for polycythemia vera, *1966*: Nov., 1506
  - for rheumatoid arthritis, *1968*: May, 696, **747-757**
  - in Memorial Hospital formulary, *1966*: May, 858, 861
- Allergic emergencies, *1966*: Sept., **1313-1324**
  - management, *1966*: Sept., 1317
  - prophylaxis, *1966*: Sept., 1322
- Allergy. See also *Hypersensitivity.*
  - drug, cutaneous, *1967*: July, **1073-1078**
  - food, *1966*: March, 397
- Allopurinol, for gout, *1967*: Sept., 1217
  - to inhibit uric acid production, *1966*: May, 816, Nov., 1634
- Alpha-adrenergic receptors. See *Adrenergic receptors.*
- Alpha cells of pancreas, hyperplasia, *1968*: March, 299
  - tumors, *1968*: March, 298
- Alseroxylon, for hypertension, *1967*: Jan., 31
- Alveolar air equation, *1967*: March, 423
- Alveolar ventilation, disturbances, *1967*: March, **403-425**
  - methods of calculating, *1967*: March, 422
- Alveolar-capillary block syndrome, *1967*: *March*, 435
  - in diffuse interstitial pulmonary fibrosis, *1967*: March, 444
- Alveolitis, fibrosing, *1967*: March, 440
- Amebic dysentery, current problems, *1967*: May, **609-615**
- Amenorrhea, adrenal disorders and, *1968*: March, 344
  - hypopituitarism and, *1968*: March, 342
  - hypothalamus and, *1968*: March, 340
  - nutritional factors in, *1968*: March, 341
  - ovarian disorders and, *1968*: March, 345
  - ovarian failure and, *1968*: March, 346
  - psychologic aspects, *1967*: Nov., 1376
  - secondary, *1968*: March, **339-355**
    - diagnosis, *1968*: March, 347-354
    - estrogen-progesterone test in, *1968*: March, 349
    - factors in, *1968*: March, 339
    - progesterone test for, *1968*: March, 349
    - treatment, *1968*: March, 354-355
  - thyroid disorders and, *1968*: March, 343
  - uterine failure and, *1968*: March, 347
- Amethopterin. See *Methotrexate.*
- Amicar. See *Epsilon-aminocaproic acid.*
- Amines, sympathomimetic, adrenergic receptors and, *1968*: Sept., 1010
- Aminocaproic acid, in fibrinolysis and fibrinogenolysis, *1967*: July, 1067, Sept., 1245
  - pharmacology, *1966*: Nov., 1669
  - treatment with, complications, *1966*: Nov., **1669-1678**
- Aminophylline for status asthmaticus, *1967*: March, 380
- Aminopyrine, site of action, *1968*: Jan., 8
- Aminosalicylic acid in tuberculosis, *1966*: Sept., 1436, 1437
- Amitriptyline for alcoholism, *1967*: Sept., 1254
- Ammonia, blood, test for, *1968*: Nov., 1412
  - intoxication, bleeding esophageal varices and, *1968*: Nov., 1459
  - toxicity, hepatic coma and, *1968*: Nov., 1477
- Amphetamines, as antidepressants, *1967*: Nov., 1460
  - sympathomimetic effects, *1967*: July, 984
- Amphotericin B, for bacterial endocarditis, *1968*: Sept., 1098
  - for fungus infections, *1967*: Sept., 1184, 1187
  - for pulmonary mycoses, *1967*: March, 526
  - toxic reactions, *1967*: July, 926
- Ampicillin, *1967*: Sept., 1113, 1128-1131, 1135

- Ampicillin (*Continued*)
  - for bacterial endocarditis, *1968*: Sept., 1098
  - for chronic bronchitis, *1967*: Sept., 1170
  - for H. influenzae infections, *1967*: March, 546
  - toxic reactions, *1967*: July, 931
- Amyl nitrite, as aid to cardiac auscultation, *1966*: Jan., 77, 86
- Amyloid, Congo red test for, *1968*: May, 650
  - nature of, *1968*: May, 644-646
- Amyloidosis, cardiac, "stiff heart" syndrome due to, *1967*: July, 959
  - nerve biopsy in diagnosis, *1968*: July, 891
  - neuropathy and, *1968*: July, 906
  - orthostatic hypotension and, *1968*: July, 812
  - with rheumatoid arthritis, *1967*: July, 1025, *1968*: May, 619, **643-653**
    - clinical aspects, *1968*: May, 647-649
    - diagnosis, *1968*: May, 649-651
    - treatment, *1968*: May, 651-652
- Amyotrophic lateral sclerosis, speech disturbances in, *1968*: July, 838-842
- Amyotrophy, neuralgic, *1968*: July, 776-777
- Analgesics, cervical block, in office, *1968*: Jan., 181
  - field block, in office, *1968*: Jan., 179
  - in labor, indications for, *1968*: Jan., 138
    - techniques of administering, *1968*: Jan., 138-145
  - infiltration, in office, *1968*: Jan., 179
  - inhalational, for postoperative pain, *1968*: Jan., 88
    - in labor, *1968*: Jan., 141
  - intercostal block, in office, *1968*: Jan., 180
  - local, in office, *1968*: Jan., 174-177
  - narcotic, *1968*: Jan., **33-45**
    - dependence on, *1968*: Jan., 33-36
    - duration of action, *1968*: Jan., 42
    - for postoperative pain, *1968*: Jan., 85
    - in children, *1968*: Jan., 132
    - in labor, *1968*: Jan., 140
    - oral administration, *1968*: Jan., 41
    - potency and efficacy, *1968*: Jan., 39
    - regulations of use, *1968*: Jan., 36
    - selection, *1968*: Jan., 39-44
  - nephropathies due to, *1966*: **1085-1090**
  - non-narcotic, for postoperative pain, *1968*: Jan., 87
    - mechanisms of action, *1968*: Jan., **3-14**
    - new, *1968*: Jan., 38
    - site of action, *1968*: Jan., 8-13
  - regional, in labor, *1968*: Jan., 142
    - in office, *1968*: Jan., 179
- Analgesics (*Continued*)
  - systemic, in labor, *1968*: Jan., 138
  - topical, in office, *1968* Jan., 178
- Anamnesis, associative, of Deutsch, modified, *1967*: Nov., **1381-1397**
- Anaphylaxis, *1966*: Sept., 1314
  - clinical manifestations, *1966*: Sept., 1315
  - pathophysiology, *1966*: Sept., 1216
  - treatment, *1966*: Sept., 1317
- Anastomosis, portacaval, emergency, for bleeding esophageal varices, *1968*: Nov., 1467
    - prophylactic, for esophageal varices, *1968*: Nov., 1470
- Androgens as anticancer agents, *1966*: May, 859, 865
  - erythropoiesis and, *1968*: March, 232
  - in carcinoma of breast, *1966*: Sept., 1461
  - influence on renal function, *1966*: July, 992
  - leukopoiesis and, *1968*: March, 239
- Anemia. See also *Erythropoiesis.*
  - Biermer's. See *Anemia, pernicious.*
  - classification, pathogenic, *1966*: Nov., **1679-1687**
  - diagnosis, clinical laboratory in, *1966*: Nov., **1689-1702**
  - due, to bone marrow hypofunction, *1966*: Nov., 1679
    - to diminished hemoglobin synthesis, *1966*: Nov., 1681
    - to diminished red cell production, *1966*: Nov., 1679
    - to inordinate loss of circulatory red cells, *1966*: Nov., 1683
    - to vitamin deficiencies, *1966*: Nov., 1679
  - hemolytic, acquired, incompatibility problems in, *1966*: Nov., 1647
    - autoimmune, in elderly, splenectomy for, *1966*: Nov., 1555
    - cold agglutinins in, *1966:* Nov., 1646
    - Coombs-negative, diagnostic tests, *1966*: Nov., 1700
    - leukoerythroblastosis in, *1966*: May, 781
    - prosthetic heart valves and, *1968*: Sept., 1138
    - with acquired defects of red cells, *1966*: Nov., 1684
    - with genetically defective red cells, *1966*: Nov., 1683
  - hypochromic, *1966*: Nov., 1681
    - laboratory findings, *1966*: Nov., 1691
  - hypoplastic, *1966*: Nov., 1680
    - platelet transfusions in, *1966*: Nov., 1563
  - hypothyroidism and, *1968*: March, 235
  - in Bartonella bacilliformis infections, *1966*: Nov., 1708

- Anemia (*Continued*)
  - in cancer, effects on heart, *1966*: May, 742
  - in Clostridium welchii infections, *1966*: Nov., 1708
  - in folic acid deficiency, *1966*: Nov., 1679
  - in gluten enteropathy, *1966*: March, 521
  - in liver disease, *1966*: March, **543-549**
  - in malaria, *1966*: Nov., 1708
  - in pyridoxine deficiency, *1966*: Nov., 1682
  - in renal failure, chronic, *1966*: July, 1183
  - in rheumatoid arthritis, *1968*: May, **527-532**, 543
    - complicated, *1968*: May, 529-530
    - management, *1968*: May, 530-531
    - simple chronic, *1968*: May, 527-529
  - in syphilis, *1966*: Nov., 1709
  - in tuberculosis, *1966*: Nov., 1706
  - in ulcerative colitis, *1966*: March, 536
  - in viral infections, *1966*: Nov., 1705, 1708
  - in vitamin B_{12} deficiency, *1966*: Nov., 1679
  - iron deficiency, *1966*: Nov., 1682
    - treatment, *1966*: Nov., 1716
  - leukoerythroblastic, *1966*: May, **779-790**
  - macrocytic, laboratory diagnosis, *1966*: Nov., 1693
  - megaloblastic, *1966*: Nov., 1679
    - biochemistry, *1966*: Sept., 1246
    - hemolytic aspects, *1966*: Sept., 1248
    - laboratory diagnosis, *1966*: Nov., 1693
    - leukoerythroblastosis in, *1966*: May, 782
    - morphology, *1966*: Sept., 1245
    - nutritional, etiologic considerations, *1966*: Sept., **1245-1256**
      - metabolic effects of vitamin B_{12} therapy in, *1966*: Nov., 1628, 1630
  - microcytic, laboratory findings, *1966*: Nov., 1691
  - myelophthisic, *1966*: Nov., 1679
  - normoblastic, laboratory diagnosis, *1966*: Nov., 1695
  - of infection, *1966*: Nov., **1703-1712**
  - pernicious, genetic factors in, *1968*: Nov., 1277
    - historical notes relating particularly to Biermer's cases, *1966*: Nov., **1611-1626**
    - intrinsic factor antibodies and, *1968*: Nov., 1288
    - metabolic effects of vitamin B_{12} therapy in, *1966*: Nov., 1628, 1629
    - parietal cell antibody and, *1968*: Nov., 1286
- Anemia (*Continued*)
  - refractory, in hypernephroma, *1966*: 1069
  - sickle cell, aplastic crisis in, *1966*: Nov., 1529
    - clinical manifestations and treatment, *1966*: Nov., **1519-1532**
  - treatment, errors in, *1966*: Nov., **1713-1720**
- Anesthesia, epidural, for pain, *1968*: Jan., **209-215**
- Anesthetics, local, for postoperative pain, *1968*: Jan., 87
- Aneurysms, aortic, abdominal, *1967*: Jan., 205, 207, 208
      - diagnosis, errors in, *1966*: July, 1029
      - kidney and, *1966*: July, **1021-1030**
    - ascending, with cystic medionecrosis, *1968*: Sept., **1145-1156**
    - serum enzymes in, *1966*: Jan., 186
    - thoracic, *1967*: Jan., 199, 202
    - thoracoabdominal, *1967*: Jan., 209
  - of basilar artery, cerebellopontine angle syndrome and, *1968*: July, 792
  - intracranial, hemorrhagic stroke and, *1968*: Sept., 1200
    - treatment for, *1968*: Sept., 1209
  - renal artery, *1967*: Jan., 60
  - ventricular, causes of and surgery for, *1968*: Sept., 1122-1124
    - in coronary artery disease, *1967*: July, 945
- ANFl-Liver test, for antinuclear factors, *1968*: May, 561
- ANFl-WBC test, for antinuclear factors, *1968*: May, 561
- Angiitis, hypersensitivity, vs. juvenile rheumatoid arthritis of acute onset, *1968*: May, 575
- Angina, before myocardial infarction, *1968*: Sept., 1062
  - nocturnal, paroxysmal, *1967*: July, 944
  - of cervical root syndrome, *1967*: July, 1029
  - pectoris, adrenergic receptor blockers for, *1968*: Sept., **1031-1039**
    - carotid sinus nerve stimulation for, *1968*: Sept., 1036
    - in coronary artery disease, *1967*: July, 941, 944
    - propanolol for, *1968*: Sept., 1031
    - serum enzymes in, *1966*: Jan., 181
  - visceral, surgical treatment, *1967*: Jan., 219, 224
- Angiocardiography, *166*: Jan., **127-139**
- Angiography, fluorescein, of ocular fundus, *1968*: July, **853-869**
  - hepatic, for cancer diagnosis, *1966*: May, 757
  - in aortic disease, *1967*: Jan., 195

Angiography (*Continued*)
  in pulmonary embolism, *1967*: Jan., 181
  pancreatic, for cancer diagnosis, *1966*: May, 759
Angiokeratoma, diffuse, of Fabry, abdominal pain and, *1968*: Nov., 1277
Angioneurotic edema, hereditary, *1966*: March, 399
Angiotensin, activation, *1968*: March, 264
  as pressor agent, *1967*: July, 992
  effects, *1968*: March, 267
  in production of hypertension, *1967*: Jan., 4
  inactivation, *1968*: March, 266
  infusion test for hypertension, *1967*: July, 867
  proposed physiological action, *1968*: March, 269
  salt excretion and, *1968*: March, 276
Anhidrosis, with congenital insensitivity to pain, *1968*: July 899
Animal models, adjuvant arthritis in, *1968*: May, 669-671
  infectious arthritis in, *1968*: May, 667-669
  of rheumatoid arthritis, *1968*: May, **667-672**, **677-686**
    immunological processes and, *1968*: May, 669-671
Anisocoria, contraction, alternating, *1968*: July, 878
  third nerve paresis and, *1968*: July, 880
Ankle, in rheumatoid arthritis, surgery, *1968*: May, 729
Ankylosing spondylitis. See *Spondylitis, ankylosing.*
Ankylosis, bony, in rheumatoid arthritis, *1968*: May, 663
  of joints, in rheumatoid arthritis, *1968*: May, 614
Anorexia, agrypnotic drugs and, *1968*: July, 785-786
  in digitalis intoxication, *1966*: March, 501
  in hyperthyroidism, *1966*: March, 584
  in renal failure, *1966*: March, 510
  nervosa, amenorrhea and, *1968*: March, 341
Anoxia. See *Hypoxia*
Antabuse, *1967*: Sept., 1256
Antacids, proprietary, systemic alkalosis and hypercalcemia due to, *1966*: March, 570
Antepar, *1967*: Sept., 1205
Antibiotics. See also under specific preparations.
  as aerosols, *1967*: March, 312
  for bacterial endocarditis, *1968*: Sept., 1097, 1098
Antibiotics (*Continued*)
  for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1148
  for rheumatic fever, preventive use, *1966*: Jan., 279-285
  for tropical sprue, *1968*: Nov., 1379
  for urinary tract infection, *1966*: July, 1134
  new, for infections due to gram-negative bacilli, *1967*: Sept., **1127-1152**
  renal complications, *1966*: Jan., 266
  toxic reactions, *1967*: July, 928
Antibody(ies), anticolon, ulcerative colitis and, *1968*: Nov., 1291
  in immunoglobulin synthesis, *1966*: Nov., 1488, 1490
  intrinsic factor, gastrointestinal disease and, *1968*: Nov., 1287
  liver disease and, *1968*: Nov., 1289
  parietal cell, gastrointestinal disease and, *1968*: Nov., 1286
  synthesis, antibody as regulator, *1966*: Nov., 1492
Anticancer agents, selection, for inclusion in Memorial Hospital formulary, *1966*: May, **857-868**
Anticoagulants, for coronary artery disease, *1967*: Jan., 130
  for hemorrhagic diathesis, *1966*: Nov., 1673
  for polycythemia vera, *1966*: Nov., 1514
  for refractory heart failure, *1968*: Sept., 1165
  for stroke, *1967*: Jan., 110
  for thromboembolism, *1967*: Jan., 151
  renal complications, *1966*: Jan., 266
Anticonvulsants, *1968*: July, 963
  for trigeminal neuralgia, *1968*: July, 798
  side effects, *1968*: July, 969
Antidepressant drugs, *1967*: Nov., 1460
Antidiuretic hormone. See *Hormone, antidiuretic.*
Antifibrinolytic therapy, *1967*: July, 1067, Sept., 1244
Antifungal agents, toxic reactions, *1967*: July, 926
Antigen(s), in immunoglobulin synthesis, *1966*: Nov., 1490
  organic, inhaled, pulmonary granulomatosis due to, *1967*: March, **459-482**
  specific, of malignant tumors and leukemias, *1966*: May, **901-912**
Antigen-antibody reactions, rheumatoid arthritis inflammation and, *1968*: May, 630-631
Antihemophilic factor, preparations, in coagulation defects, *1967*: Sept., 1243
Antihistamines for status asthmaticus, *1967*: March, 388

Antihypertensive drugs, *1967*: Jan., 29, July, 985, 987
  emergency, *1967*: Jan., 35
  mild and potent, *1967*: Jan., 30, 32
Anti-inflammatory drugs, for rheumatoid arthritis, *1968*: May, 691-696
Antimalarials, for autoimmune diseases, *1966*: March, 408
  for light sensitivity, *1966*: Sept., 1309
  for rheumatoid arthritis, *1968*: May, 692, **759-764**
    juvenile, *1968*: May, 586
Antimetabolites, in Memorial Hospital formulary, *1966*: May, 859-863
Antimicrobial drugs, toxic reactions, *1967*: July, **925-940**
Antinuclear factors in rheumatoid arthritis, tests for, *1968*: May, 547, **559-565**
Anus, area of, topical analgesia, *1968*: Jan., 179
  and rectum, anomalies of, inheritance of, *1968*: Nov., 1274
Anxiety, cardiovascular response to, adrenergic receptor blockers and, *1968*: Sept., 1043
  in children, *1967*: Nov., 1434
  in chronic illness, *1967*: Nov., 1404
  internist's role, *1967*: Nov., 1417
  tranquilizers in, *1967*: Nov., 1455, 1457
Aorta, abdominal, occlusive disease, *1967*: Jan., 210
  anatomy, *1967*: Jan., 193
  aneurysms, abdominal, *1967*: Jan., 205, 207, 208
      diagnosis, errors in, *1966*: July, 1022
      kidney and, *1966*: July, **1021-1030**
    serum enzymes in, *1966*: Jan., 186
  ascending, cystic medionecrosis and aneurysmal dilatation, *1968*: Sept., **1145-1156**
  coarctation, *1967*: Jan., 196
    diagnosis, *1967*: Jan., 19; *1968*: Sept., 1216
    hypertension in, *1966*: Jan., 293; *1967*: July, 971
    in adult, clinical picture, *1966*: Jan., 28
    pathology, *1966*: Jan., 10
    phonocardiogram in, *1966*: Jan., 105
  diseases, angiographic study, *1967*: Jan., 195
    recognition and management, *1967*: Jan., **193-214**
  hypoplasia, pathologic complexes, *1966*: Jan., 11
  insufficiency, phonocardiogram in, *1966*: Jan., 84, 107
  regurgitation, phonocardiogram, *1966*: Jan., 107
Aorta (*Continued*)
  stenosis, congenital, angiocardiography in, *1966*: Jan., 131
    in adult, clinical picture, *1966*: Jan., 25, 26
    phonocardiogram in, *1966*: Jan., 85, 100
    postextrasystolic beats in, *1966*: Jan., 69
    surgical indications and treatment, *1966*: Jan., **309-323**
  terminal, occlusion of, sudden, *1967*: Jan., 211
  thoracic, aneurysms, *1967*: Jan., 199, 202
    congenital anomalies, *1967*: Jan., 196
  thoracoabdominal, aneurysms, *1967*: Jan., 209
    congenital anomalies, *1967*: Jan., 196
    obstructing lesions, *1967*: Jan., 204
Aortic arch, obstructing lesions, *1967*: Jan., 204
Aortic sinus in production of hypertension, *1967*: Jan., 8
Aortic-pulmonary window, phonocardiogram, *1966*: Jan., 106
Aortoenteric fistula, *1967*: Jan., 212
Aortovenous fistulas, *1967*: Jan., 213
Appendicitis, pain pattern in, *1968*: Jan., 104
Apresoline. See *Hydralazine.*
Aralen. See *Chloroquine.*
Aramine. See *Metaraminol.*
Arboviruses, encephalitis due to, in Middle Atlantic states, *1967*: May, **661-671**
  infections due to, immunoprophylaxis, *1967*: May, **673-679**
ARD, *1967*: May, 811
  in military forces, *1967*: May, **769-779**
Arginine vasopressin, secretion, *1968*: March, 381. See also *Hormone, antidiuretic.*
Argyll Robertson pupil, *1968*: July, 879
Aristocort. See *Triamcinolone.*
Arm, local analgesia of, in office, *1968*: Jan., 180
  nerve blocks in, *1968*: Jan., 124
  pain in, neurologic disorders and, *1968*: July, **773-779**
Armenian disease, *1966*: March, 373
Arrhythmia, cardiac, analysis, ectopic beats in, *1966*: Jan., 62
  beta-adrenergic receptor blocking drugs for, *1968*: Sept., **1017-1029**
  in coronary artery disease, *1967*: July, 942
  integrated approach to, *1967*: Sept., 1228
  newer drugs in, *1967*: Sept., **1223-1240**

Arrhythmia *(Continued)*
  cardiac, potassium therapy in, *1968*: Sept., 1105
    propanolol for, *1968*: Sept., 1020-1026
    prosthetic heart valves and, *1968*: Sept., 1138
    quinidine in, *1966*: Sept., 1225
    serum enzymes in, *1966*: Jan., 186
    ventricular, after myocardial infarction, *1968*: Sept., 1068
Arsenic poisoning, neuropathy and, *1968*: July, 905
Arterial occlusion, retinal, fluorescein angiography in, *1968*: July, 866
Arterial trunks, transposition, corrected, clinical picture, *1966*: Jan., 30
    pathology, *1966*: Jan., 8
Arteriography, coronary, *1966*: Jan., 138
    in cerebrovascular disease, *1967*: Jan., 119
  renal, *1967*: Jan., **47-67**
Arteriovenous fistula, angiocardiography in, *1966*: Jan., 137
  phonocardiogram in, *1966*: Jan., 104
Arteritis, rheumatoid arthritis and, *1968*: May, 618
Artery(ies), basilar, aneurysm of, cerebellopontine angle syndrome and, *1968*: July, 792
  cerebral, hemorrhagic stroke and, *1968*: Sept., 1200, 1204
    malformations of, hemorrhagic stroke and, *1968*: Sept., 1202
  occlusive disease, pathophysiology, *1967*: Jan., 215
    reconstructive surgery for, *1967*: Jan., **215-225**
  renal, stenosis, diagnosis, *1968*: Sept., 1217
      treatment, *1968*: Sept., 1229
Arthritis, adjuvant, in animals, *1968*: May, 669-671
  gouty. See also *Gout.*
  in hyperparathyroidism, *1967*: July, 878
  in ulcerative colitis, *1966*: March, 529; *1967*: July, 1012
  infectious. See *Arthritis, septic.*
  of hypogammaglobulinemia, *1968*: May, 578
  psoriatic vs. rheumatic, *1968*: May, 506-507
  rheumatoid, acromioclavicular joint in, *1968*: May, 497
    alkylating agents for, *1968*: May, 696, **747-757**
    amyloidosis with, *1968*: May, 619, **643-653**
    anemia in, *1968*: May, **527-532**, 543
    animal models for, *1968*: May, **667-672, 677-686**
Arthritis (*Continued*)
  rheumatoid, anti-inflammatory drugs for, *1968*: May, 691-696
    antimalarial therapy for, *1968*: May, 692, **759-764**
    antinuclear factor tests in, *1968*: May, 547, **559-565**
    arteritis and, *1968*: May, 618
    articular cartilage in, *1968*: May, 660
    azathioprine for, *1968*: May, 751
    bacteria and, *1968*: May, 674
    bed rest for, *1968*: May, 689, 700
    bedsoniae and, *1968*: May, 676
    betamethasone for, *1968*: May, 743
    blood abnormalities in, *1968*: May, 543-544
    bone changes in, *1968*: May, 661, 663
    cartilage destruction and, *1968*: May, 611
    chloroquine for, *1968*: May, 761
    chronic BFP test for syphilis in, *1966*: Sept., 1275
    chrysotherapy for, *1968*: May, **733-738**
    connective tissue cell changes and, *1968*: May, 598-600
    corticosteroids for, *1968*: May, 693, **739-746**
    cortisone for, *1968*: May, 743
    course of, intermittent, *1968*: May, 551-552
      remissions in, *1968*: May, 552-554
    cyclophosphamide for, *1968*: May, 696, 750, 751
    cytotoxic drugs for, *1968*: May, 696, **747-757**
    dexamethasone for, *1968*: May, 743
    diagnosis of, criteria for, *1968*: May, 480
      differential, *1968*: May, **503-515**
        ankylosing spondylitis in, *1968*: May, **517-526**
      laboratory studies in, *1968*: May, **539-548**
    drugs in, *1967*: Sept., **1213-1222**
    elbow in, *1968*: May, 496
    epidemiology, *1968*: May, **479-491**
      familial factors in, *1968*: May, 489-490
      genetic factors in, *1968*: May, 489-490
      methods of examination in, *1968*: May, 479
      rheumatoid factor and, *1968*: May, 487-488
    erythrocyte sedimentation rate in, *1968*: May, 543
    etiology of, infectious, *1968*: May, **673-676**
    foot in, *1968*: May, 498

Arthritis (*Continued*)
  rheumatoid, gold therapy for, *1968*: May, **733-738**
    granuloma in, *1968*: May, 616
    hand in, *1968*: May, 495
    hip in, *1968*: May, 501
    hydrocortisone for, *1968*: May, 743
    hydroxychloroquine for, *1968*: May, 761
    hypercortisonism and, *1968*: May, 740-742
    immunological factors in, *1968*: May, 594-598
    indomethacin for, *1968*: May, 694
    infectious agents and, *1968*: May, 598
    inflammation in, *1968*: May, 611, **623-634**
      antigen-antibody reactions, *1968*: May, 630-631
      cellular responses, *1968*: May, 629-630
      chemical mediators, *1968*: May, 624-626
      complement system and, *1968*: May, 628-629
      immune factors, *1968*: May, 630-631
      kallikrein-kininogen-kinin system and, *1968*: May, 624
      lysosomes and, *1968*: May, 626-628, 637
      neutrophils and, *1968*: May, 629
      polymorphonuclear leukocytes and, *1968*: May, 629
      vascular reactions, *1968*: May, 629
      vasoactive amines and, *1968*: May, 625
    joint ankylosis and, *1968*: May, 614
    joint aspiration in, *1968*: May, 539
    joint effusion in, *1968*: May, 609
    joint space narrowing in, *1968*: May, 660
    juvenile, antimalarial therapy for, *1968*: May, 586
      aspirin for, *1968*: May, 584
      corticosteroids for, *1968*: May, 585
      course, *1968*: May, 581-583
      early natural history, *1968*: May, **567-591**
      gold therapy for, *1968*: May, 586
      management, *1968*: May, 583-587
      modes of onset, *1968*: May, 568
      prognosis in, *1968*: May, 587
    knee in, *1968*: May, 499
    laboratory tests in, *1968*: May, **539-548**
    leukocytosis in, *1968*: May, 543
    low back pain and, *1968*: Jan., 64
    lung lesions in, *1968*: May, 619
    lymph node hyperplasia in, *1968*: May, 619

Arthritis (*Continued*)
  rheumatoid, lymphoid nodules of joints in, *1968*: May, 610
    lysosomal enzymes and, *1968*: May, 600-601
    lysosomes and, *1968*: May, 637-638
    malalignment of joints in, *1968*: May, 660
    management of, conservative, *1968*: May, **699-702**
      orthopedic, *1968*: May, 696-697
    metabolic changes in, *1968*: May, 601
    metatarsophalangeal joints in, *1968*: May, 498
    methotrexate for, *1968*: May, 750, 754
    methylprednisone for, *1968*: May, 743
    mycoplasmas and, *1968*: May, 675
    myositis in, *1968*: May, 619
    nitrogen mustard for, *1968*: May, 696, 750
    orthopedic surgery for, *1968*: May, **717-731**
    osteoarthrosis in, secondary, *1968*: May, 663
    osteoporosis in, *1968*: May, 656
    pannus formation in, *1968*: May, 611
    pathogenesis, *1968*: May, **593-605**
      lysosomes and, *1968*: May, **635-641**
    pathology, *1968*: May, **607-621**
    phenylbutazone for, *1968*: May, 694
    physical signs in, *1968*: May, **493-502**
    physical therapy for, *1968*: May, 701, **707-716**
    prednisone and prednisolone for, *1968*: May, 693, 743
    prevalence, *1968*: May, 482-487
    prognosis, favorable factors in, *1968*: May, 555
    pulmonary lesions in, *1968*: May, 619
    radiologic manifestations, *1968*: May, **655-665**
    rehabilitation in, *1968*: May, 713-714
    rheumatoid factor in, tests for, *1968*: May, 545
    salicylate therapy for, *1968*: May, 699, **703-706**
    serologic tests in, *1968*: May, 544-547
    seropositive, nodular, optimum therapeutic program in, *1968*: May, **687-698**
      vs. seronegative, *1968*: May, **533-538**
    serum abnormalities in, *1968*: May, 543-544, **559-565**
    shoulder in, *1968*: May, 497
    soft tissue changes in, *1968*: May, 656
    spine in, *1968*: May, 501
    splints and appliances for, *1968*: May, 712-713
    sternoclavicular joint in, *1968*: May, 497

- Arthritis (*Continued*)
  - rheumatoid, subluxation of joints in, *1968*: May, 660
    - symposium on, *1968*: May, **477-764**
    - synovial fluid examination in, *1966*: Sept., 1288, 1290, 1291; *1968*: May, 539-543
    - synovitis in, acute, *1968*: May, 608
    - systemic nature, *1968*: May, 493
    - triamcinolone for, *1968*: May, 743
    - types of course and prognosis in, *1968*: May, **549-557**
    - uncommon manifestations, *1967*: July, **1019-1026**
    - variants, *1968*: May, **503-515**
    - vs. gout, *1967*: July, 1036
    - vs. progressive systemic sclerosis, *1968*: May, 560, 562
    - vs. systemic lupus erythematosus, *1968*: May, 560, 562
    - viruses and, *1968*: May, 675
    - with leukopenia, *1968*: May, 529
    - with psoriasis, *1968*: May, 506-507
    - with splenomegaly, *1968*: May, 529
    - with ulcerative colitis, *1968*: May, 507-509
    - with urethritis and conjunctivitis, *1968*: May, 504-505
  - septic, in animals, *1968*: May, 667-669, **677-686**
    - synovianalysis in, *1966*: Sept., 1288, 1291
    - vs. juvenile rheumatoid arthritis of monarticular onset, *1968*: May, 580
  - synovial fluid evaluation in, *1966*: Sept., **1281-1293**
  - traumatic, vs. juvenile rheumatoid arthritis of monarticular onset, *1968*: May, 580
  - tuberculous, vs. juvenile rheumatoid arthritis of monarticular onset, *1968*: May, 580
- Arthropathy, intestinal disease with, *1966*: March, **417-425**
- Ascites, chylous, lymphangiography in, *1967*: Jan., 234, 243
- Aspergillosis, pulmonary, *1967*: March, **519-527**
- Aspiration, of synovial fluid, *1966*: Sept., 1282
  - smears, for cancer diagnosis, *1966*: May, 662
- Aspirin. See also *Salicylates.*
  - for juvenile rheumatoid arthritis, *1968*: May, 584
  - for rheumatism, *1967*: Sept., 1213
  - site of action, *1968*: Jan., 8
- Asthma, bronchial, emphysema and, relationship, *1967*: March, 275
  - intractable, management, current concepts, *1967*: March, **373-389**
- Asthma (*Continued*)
  - bronchial, pathophysiology and pathology, *1967*: March, 374, 375
- Astrocytoma, cerebellopontine angle syndrome and, *1968*: July, 792, 793
- Ataractics, in labor, *1968*: Jan., 141
- Ataxia, Friedreich's, *1968*: July, 900
- Atherosclerosis, cerebral, *1967*: Jan., 116
  - electron microscopic studies, *1967*: Jan., 146
  - of coronary artery, anticoagulant therapy, *1967*: Jan., 130
    - dietary treatment, *1967*: Jan., 126
  - of renal artery, *1967*: Jan., 54
  - prevention and treatment, current knowledge, *1967*: Jan., **97-104**
  - role of cholesterol and polyunsaturated fats in, *1967*: Jan., 126
- Athetosis, speech disturbances in, *1968*: July, 838-841
- Atrial fibrillation and flutter, electrical conversion in, *1966*: Jan., **117-125**
  - propanolol for, *1968*: Sept., 1020, 1023
- Atrial septal defects, in adults, clinical features, *1966*: Jan., 19
  - manifestations, *1967*: July, **949-957**
- Atrioventricular block, complete, pacemakers in, *1966*: Jan., 326
- Atromid S. See *Clofibrate.*
- Atropine, for hypertension, *1967*: July, 990
  - for slow ventricular rate, *1968*: Sept., 1070
  - for status asthmaticus, *1967*: March, 380
- Auricular nerve, greater, biopsy, *1968*: July, 886
- Auscultation, cardiac, *1966*: Sept., 1210
  - functional tests as aid, *1966*: Jan., **73-89**
  - in atrial septal defects, *1967*: July, 953
  - relationship with phonocardiography, *1966*: Jan., 91
- Autohemolysis in anemias, *1966*: Nov., 1700
- Autoimmune diseases, acute renal failure due to, *1967*: July, 996
  - chronic biologic false-positive test for syphilis in, *1966*: Sept., **1271-1279**
  - gastrointestinal, *1966*: March, 400-406
    - treatment, *1966*: March, 406
- Autoimmune factors in emphysema, *1967*: March, 278
- Autoimmunity, gastrointestinal disease and, *1968*: Nov., **1285-1295**
- Automatisms, features, *1968*: July, 961
- Autonomic blockade, neurolytic agents for, *1968*: Jan., 163
  - in hypertension, *1967*: July, 989

Autonomic nervous system, hypertension and, *1967: July, 977*
Avitaminosis. See under *Vitamins.*
Azathioprine, for immune suppression, in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1150
  in renal transplantation, *1966*: July, 1167
  for rheumatoid arthritis, *1967*: Sept., 1221; *1968*: May, 751
Azotemia, drugs causing, *1966*: March, 570
  in cancer, *1966*: May, 726
  in lupus nephritis, *1966*: July, 1121
  of gastrointestinal bleeding, *1966*: March, 512
  prerenal, secondary to congestive heart failure, *1966*: Jan., 258
  vs. renal, differential diagnosis, *1966*: July, 1000

BACK, braces, types, functions, and how to order and use them, *1967*: Sept., **1315-1343**
  lower, pain in, *1968*: Jan., **55-71**
Bacteremia, staphylococcal, penicillins in, *1967*: Sept., 1116, 1120
Bacteria, rheumatoid arthritis and, *1968*: May, 674
  sensitivity to, tests for, *1966*: Sept., 1430
Bacteriuria, in chronic renal failure, *1966*: July, 1184
  in urinary tract infection, *1966*: July, 1130
Bacteroides infections, postoperative, in cancer patients, treatment, *1966*: May, 799
Bagassosis, *1967*: March, 459, 460, 478
Balloon tamponade, for bleeding esophageal varices, *1968*: Nov., 1466
Banti syndrome in elderly, splenectomy for, *1966*: Nov., 1541
Barbiturates, for pain, *1968*: Jan., 49
  for seizures, *1968*: July, 963
  in labor, *1968*: Jan., 139
Bartonella bacilliformis infection, anemia, *1966*: Nov., 1708
Basal metabolic rate, thyroid function and, *1968*: March, 463
BCG substrains, differential characteristics, *1967*: May, 756
BCG vaccination, *1967*: May, **753-764**
Bed rest. See under *Rest.*
Bedsoniae, rheumatoid arthritis and, *1968*: May, 676
Belts, sacroiliac, *1967*: Sept., 1336
Benemid. See *Probenecid.*
Benzodiazepenes as tranquilizers, *1967*: Nov., 1455
Benzothiadiazine diuretics in hypertension, *1967*: Jan., 30
  therapy, potassium and, *1968*: Sept., 1105
Benzyl penicillin, toxic reactions, *1967*: July, 929
Beriberi heart disease, *1966*: Jan., 303
Beta-adrenergic receptors. See *Adrenergic receptors.*
Beta cells of pancreas, tumors, *1968*: March, 300
Beta-lipoprotein deficiency, congenital, *1968*: Nov., 1277
Betamethasone, for rheumatoid arthritis, *1968*: May, 743
Beta sympathetic blocking agents in cardiac arrhythmias, *1967*: Sept., 1223
Biermer's anemia, historical notes, *1966*: Nov., **1611-1626**. See also *Anemia, pernicious.*
Bile pigment excretion, test for, *1968*: Nov., 1412
Bile salts, implications of current research on, *1968*: Nov., 1271
Biliary tract, carcinoma, diagnosis, newer techniques, *1966*: May, 756
  disease, pain pattern in, *1968*: Jan., 106
Bilirubin, metabolism, *1968*: Nov., 1417
  congenital defects in, *1968*: Nov., 1276
  serum, in diagnosis of anemias, *1966*: Nov., 1697
  test for, *1968*: Nov., 1409, 1428
Biopsy, endometrial, in amenorrhea, *1968*: March, 350
  liver, percutaneous, in cancer, *1966*: March, 756
  of nerves, *1968*: July, **885-893**
  renal, in toxemia of pregnancy, *1966*: July, 1051
  in urinary tract infection, *1966*: July, 1132
Bird breeder's (fancier's) lung, *1967*: March, 459, 477
Bisolvon in chronic bronchitis, *1967*: Sept., 1175
Bithionol, photodermatitis from, *1966*: Sept., 1302
Bladder, carcinoma, diagnosis, cytologic, *1966*: May, 657
  radiation therapy for, *1968*: Jan., 205
  function, after myocardial infarction, *1968*: Sept., 1066
Blankophores, photodermatitis due to, *1966*: Sept., 1302
Blastomycosis, of adrenal glands, *1968*: March, 329
  pulmonary, *1967*: March, **519-527**
Bleeding. See *Hemorrhage* and *Hemorrhagic.*

- Blood, abnormalites, in rheumatoid arthritis, *1968*: May, 543-544
  - in ulcerative colitis, *1966*: March, 532
    - uncommon, *1966*: March, **535-540**
  - cancer cells in, *1966*: May, 661
  - clot retraction, biomechanics, *1966*: Sept., 1266
  - clotting disturbances, in liver disease, *1966*: March, 544
  - compatibility tests, *1966*: Nov., **1643-1652**
  - coagulation. See *Coagulation.*
  - cultures, role in management of infections, *1966*: Sept., 1420
  - diseases, in aged persons, splenectomy for, *1966*: Nov., **1533-1558**
    - symposium on, *1966*: Nov., **1485-1720**
  - dyscrasias, oral manifestations, *1966*: March, 367
  - infections, hematologic disorders due to, *1966*: Nov., 1708
  - loss, in infections, anemia of, *1966*: Nov., 1709
    - leukoerythroblastosis due to, *1966*: May, 779
  - platelets. See under *Platelet.*
  - pressure, central venous, significance, *1968*: Sept., 1083
      - venomotor tone and, *1968*: Sept., **1077-1090**
    - high. See *Hypertension.*
    - low. See *Hypotension.*
    - orthostatic, *1968*: July, 809
    - taking, *1966*: Sept., 1204; *1967*: Jan., 15
  - smears, in diagnosis of anemia, *1966*: Nov., 1690
  - transfusions. See *Transfusions.*
  - vessels, diseases, symposium on, *1967*: Jan., **1-261**
    - normal and diseased, fine structure of, newer concepts, *1967*: Jan., **139-150**
    - permeability, in rheumatoid arthritis, *1968*: May, 629
  - whole, clot lysis time, test for, *1967*: July, 1066
- BMR. See *Basal metabolic rate.*
- Body fluids. See *Fluids, body.*
- Bone(s), disorders, in hyperparathyroidism, *1967*: July, 878
    - in rheumatoid arthritis, *1968*: May, 661, 663
  - metastases, in lung cancer, treatment, *1967*: March, 570
  - periosteal formation of, hyperthyroidism and, *1968*: March, **393-398**
  - rarefaction, in Graves' disease, *1967*: July, 920
  - scanning, for metastatic cancer, *1966*: May, **701-710**
- Bone(s) (*Continued*)
  - tuberculosis, *1966*: Sept., 1443
  - tumors, low back pain and, *1968*: Jan., 68
    - radiation therapy for, *1968*: Jan., 204
- Bone marrow, carcinoma, metastatic, leukoerythroblastosis in, *1966*: May, 783
  - function, in rheumatoid arthritis, *1968*: May, 528
  - infections, anemia due to, *1966*: Nov., 1704
- Bowels, function, after myocardial infarction, *1968*: Sept., 1066
- Braces, back, types, functions, and how to order and use them, *1967*: Sept., **1315-1343**
- Brachial neuritis, paralytic, *1968*: July, 776-777
- Brachial pain, neurologic disorders and, *1968*: July, **773-779**
- Brachial plexus, compression, *1968*: July, 777
  - lesions, *1968*: July, 776
- Bradykinin, activation, *1968*: March, 266
  - inactivation, *1968*: March, 267
  - salt excretion and, *1968*: March, 278
- Bradykinin peptides, pain stimulation by, *1968*: Jan., 5, 6-8
- Brain. See also *Cerebellum* and *Cerebrum.*
  - arteriovenous malformations of, hemorrhagic stroke and, *1968*: Sept., 1202
    - treatment for, *1968*: Sept., 1208
  - atherosclerosis, *1967*: Jan., 116
  - blood supply, *1967*: Jan., 114
  - cortex of, pain originating in, *1968*: Jan., 117
  - lesions, electroencephalographic patterns in, *1968*: July, 937-939
  - metastases, in lung cancer, treatment, *1967*: March, 569
  - schistosomiasis mansoni, *1966*: March, **597-602**
  - stem, astrocytoma, cerebellopontine angle syndrome and, *1968*: July, 792
  - syndrome, internist's role, *1967*: Nov., 1421
    - in aged persons, *1967*: Nov., 1519
- Breast, carcinoma, advanced, treatment, *1966*: Sept., **1457-1467**
    - diagnosis by needle aspiration smears, *1966*: May, 662
    - gastrointestinal bleeding in, *1966*: May, 748
    - late manifestations, *1967*: July, **1089-1091**
    - mortality, *1966*: May, 622
    - surgery for, Thio-TEPA as adjunct, *1966*: Sept., 1459
- Breathing, assisted and controlled, in status asthmaticus, *1967*: March, 384

Breathing (*Continued*)
  intermittent positive pressure, *1967*: March, 315-321
    in status asthmaticus, *1967*: March, 383, 384
    lung abscess following, *1967*: March, 534
  mechanics, *1966*: Jan., 150
  training, in chronic obstructive lung disease, *1967*: March, 353
Bright's disease. See *Nephritis.*
Bromodermas, circumscribed, *1967*: July, 1083
Bromsulphalein excretion test, *1968*: Nov., 1411
Bronchial asthma. See *Asthma, bronchial.*
Bronchiectasis, diagnosis and management, *1967*: March, 536
Bronchiolitis in children, *1967*: May, 824
Bronchitis, acute, in children, *1967*: May, 823
  chronic, emphysema and, clinical manifestations and their physiologic significance, *1967*: March, **283-292**
    treatment, newer drugs in, *1967*: Sept., **1169-1178**
  emphysema and, relationship, *1967*: March, 275
  viral, *1967*: May, 812
Bronchodilators, aerosol, *1967*: March, 310
  in status asthmaticus, *1967*: March, 380
Bronchogenic carcinoma. See *Lungs, carcinoma.*
Bronchopneumonia. See *Pneumonia.*
Bronchospasm, treatment, in respiratory failure, *1967*: March, 333
Bronchus, carcinoma, mortality, *1966*: May, 621
  hygiene, in chronic obstructive lung disease, *1967*: March, 350
  obstruction, in lung cancer, treatment, *1967*: March, 569
    lung abscess with, *1967*: March, 532
  suppurative diseases, *1967*: March, 536
Bronze diabetes, *1966*: Nov., 1581
Bulbar palsy, speech disturbances in, *1968*: July, 838-841
Bundle-branch block, extrasystoles in, *1966*: Jan., 54, 65
  right, phonocardiogram, *1966*: Jan., 96
Bursitis, in Graves' disease, *1967*: July, 919
  in rheumatoid arthritis, *1968*: May, 493
  pain of, radiation therapy for, *1968*: Jan., 203
Busulfan, as anticancer agent, *1966*: May, 858, 862
  for chronic granulocytic leukemia, *1966*: May, 806
Busulfan (*Continued*)
  for polycythemia vera, *1966*: Nov., 1510
Byler's disease, *1968*: Nov., 1275

CALCIUM, absorption, normal, *1968*: Nov., 1343
    studies, *1968*: Nov., 1351
  concentration, cardiovascular system and, *1968*: Sept., 1245
  imbalance, in renal failure, *1966*: July, 1180
  serum and urinary, hyperparathyroidism and, *1968*: March, 452
  tolerance test, hyperparathyroidism and, *1968*: March, 457
Calcium-47 scanning in bone metastases, *1966*: May, 702
Calcium ion, angiotensin and, *1968*: March, 268
Calculus(i), renal urate, *1966*: July, 1035
Cancer. See *Carcinoma.*
Cancer cells, electron microscopy of, *1966*: May, **887-900**
  in blood, *1966*: May, 661
Candidosis, pulmonary, *1967*: March, **519-527**
Capreomycin for drug resistant tuberculosis in children, *1967*: Sept., 1160, 1162, 1163
Carbamazepine (Tegretol), for seizures, *1968*: July, 972
  for trigeminal neuralgia, *1968*: Jan., 112; July, 799
Carbohydrates, absorption. See also *Disaccharides, absorption.*
    normal, *1968*: Nov., 1341
    studies, *1968*: Nov., 1351
  dietary, and atherosclerosis, *1967*: Jan., 99, 126
Carbon dioxide narcosis due to alveolar hypotension, treatment, *1967*: March, 420
Carbon monoxide poisoning, hyperbaric oxygen in, *1967*: Sept., 1308
Carbonic anhydrase inhibitors, for refractory heart failure, *1968*: Sept., 1173
Carcinogenesis, basic considerations, *1966*: May, 646
Carcinoid, bradykinin and, *1968*: March, 268
  malignant, *1966*: May, 739
  syndrome, cutaneous melanosis with, *1966*: March, 357
    pancreatic islet cell tumors and, *1968*: March, 305
Carcinoma, antigens of, specific, *1966*: May, **901-912**

Carcinoma (*Continued*)
  cardiovascular disturbances in, *1966*: May, **723-746**
  causes, unifying concept, *1966*: May, **869-874**
  chemotherapy, drugs employed in, *1966*: May, **857-868**
    gastrointestinal effects, *1966*: May, 751
  chromosomal alterations in, *1966*: May, **875-885**
  cigarette smoking and, *1966*: May, 638, 644, 645
  contraceptive drugs and, *1967*: Sept., 1269
  diagnosis, by radioactive isotope scanning, *1966*: May, **689-700**
    cytologic, *1966*: May, **651-666**
    lymphangiography in, *1966*: May, **675-688**
    scanning in, *1966*: May, **689-700**
  drugs for, included in Memorial Hospital formulary, *1966*: May, **857-868**
  electron microscopy in, *1966*: May, **889-900**
  en cuirasse, *1967*: July, 1090
  environmental factors, *1966*: May, **631-650**
  epidemiology, *1966*: May, 632
  fibrinolysis with hemorrhage in, *1967*: July, 1065, 1068
  fluid and electrolyte disturbances in, *1966*: May, **711-732**
  gastrointestinal, articular manifestations, *1966*: March, 422
    diagnosis, newer techniques, *1966*: May, **754-759**
    manifestations, unusual, *1966*: May, **747-754**
    metastatic, chemotherapy in, *1966*: March, **427-438**
  heredity and, *1966*: May, **875-885**
  immunoglobulins in, monoclonal, *1966*: May, **667-674**
  immunology, *1966*: May, **901-912**
  incidence data as clues to environmental factors in, *1966*: May, 633
  incitants, *1966*: May, 620, 640, 870, 872
  leukoerythroblastic anemia in, *1966*: May, **779-790**
  lymph node invasion, dynamics, *1967*: Jan., 254
  lymphangiography in, indications, techniques, and complications, *1966*: May, **675-688**
  lymphatics and, *1967*: Jan., **249-261**
  medical advances in, symposium on, *1966*: May, **611-912**
  morbidity and mortality, changing pattern, implications, *1966*: May, **613-630**

Carcinoma (*Continued*)
  mortality, age-adjusted rates for selected sites, *1966*: May, 633-637
  nonendocrine, endocrine syndromes associated with, *1966*: May, **763-778**
  oat-cell, of lung and mediastinum, *1968*: March, 323
  occupational, *1966*: May, 637, 646
  of biliary tract, diagnosis, *1966*: May, 756
  of bladder, diagnosis, *1966*: May, 657
  of bone, metastatic, scanning for, *1966*: May, **701-710**
  of breast, advanced, treatment, *1966*: Sept., **1457-1467**
    gastrointestinal bleeding in, *1966*: May, 748
    late manifestations, *1967*: July, **1089-1091**
    mortality, *1966*: May, 622
  of colon and rectum, diagnosis, *1966*: May, 659
    mortality, *1966*: May, 617
  of endometrium, diagnosis, *1966*: May, 653
    management, *1966*: May, **833-844**
  of esophagus, diagnosis, *1966*: May, 659, 754
  of fallopian tube, diagnosis, *1966*: May, 653
  of head and neck, gastrointestinal bleeding in, *1966*: May, 749
  of heart, *1966*: May, **733-746**
  of liver, diagnosis, *1966*: May, 756
    scanning in, *1966*: May, 695
    unusual aspects, *1966*: May, 753
  of lung. See under *Lung*.
  of mouth, diagnosis, *1966*: May, 658
  of ovary, advanced, management, *1966*: May, **845-856**
    diagnosis, *1966*: May, 653
    mortality, *1966*: May, 626
  of pancreas, diagnosis, *1966*: May, 658
    gastrointestinal bleeding in, *1966*: May, 748
    mortality, *1966*: May, 617
    systemic effects, *1966*: March, 457
  of prostate, diagnosis, *1966:* May, 658
    mortality, *1966*: May, 626
  of stomach, diagnosis, *1966*: May, 659, 754
    environmental factors in, *1968*: Nov., 1279
    genetic factors in, *1968*: Nov., 1279
    mortality, *1966*: May, 616, 640, 641, 642
  of thyroid gland, thyroid hormones in, *1966*: Sept., 1399
  of urinary tract, diagnosis, *1966*: May, 657

Carcinoma (*Continued*)
  of uterus, diagnosis, *1966*: May, 652
    mortality, *1966*: May, 624
  pain of, percutaneous cordotomy for, *1968*: Jan., 195
    radiation therapy for, *1968*: Jan., 206
  preventive measures, *1966*: May, 643
  radiation therapy, gastrointestinal effects, *1966*: May, 752
    preoperative, argument for, *1967*: Jan., 255
    response of lymphatic channels to, *1967*: Jan., 249
  role of lymphocytes in, *1967*: Jan., 255
  scanning in, *1966*: May, **689-700**
  surgical treatment, infections in patients undergoing, treatment, *1966*: May, **791-802**
Cardiac. See also *Heart.*
Cardiac arrhythmias. See *Arrhythmias.*
Cardiac pacemakers, clinical and physiologic studies, *1966*: Jan., **322-341**
Cardiac output, in shock, *1968*: Sept., 1050
Cardiomegaly with cyanosis and no murmurs, *1966*: Jan., 31
Cardiomyopathy. See *Myocardiopathy.*
Cardiopulmonary involvement in sickle cell anemia, *1966*: Nov., 1524
Cardiovascular disease, hypothyroidism in, *1968*: March, 440
  potassium therapy for, *1968*: Sept., **1103-1113**
  recent advances in, symposium on, *1968*: Sept., **1007-1260**
Cardiovascular disturbances in cancer, *1966*: May, **733-746**
Cardiovascular system, adrenergic receptors in, *1968*: Sept., 1010
  advanced renal disease and, *1968*: Sept., **1237-1247**
  hyperdynamic states of, adrenergic receptor blockers and, *1968*: Sept., **1041-1048**
Carotid artery surgery in stroke, *1967*: Jan., **113-122**
Carotid sinus, role, in production of hypertension, *1967*: Jan., 8
Carotid sinus nerve, stimulation of, for angina pectoris, *1968*: Sept., 1036
Carpal tunnel syndrome, *1968*: Jan., 113; July, 778-779
  in gout, *1967*: July, 1038
Cartilage, articular, destruction of, in rheumatoid arthritis, *1968*: May, 611
Cartilage fragments or reticulum fibrils in synovial fluid, *1966*: Sept., 1286
Castration. See *Oophorectomy.*
Catabolic mechanisms in control of serum immunoglobulin levels, *1966*: Nov., 1494
Cataplexy, narcolepsy and, *1968*: July, 784
Catastrophic reactions in adolescents, *1967*: Nov., 1442
Catecholamines, *1967*: July, 982
  adrenergic receptors and, *1968*: Sept., 1010
  levels, in shock, *1968*: Sept., 1051
  release, angiotensin and, *1968*: March, 268
  tests, for pheochromocytoma, *1968*: Sept., 1220
Catharsis, tracheobronchial, in status asthmaticus, *1967*: March, 378
Catheterization, cardiac. See under *Heart.*
Causalgia, *1968*: Jan., 148-151
Celiac disease. See *Sprue, nontropical.*
Cells, biology of, basic aspects, *1966*: May, 887
  cancer, electron microscopy, *1966*: May, 887-900
  cancerous changes in, *1966*: May, 872
Cephaloridine, *1967*: Sept., 1128-1131, 1147
Cephalothin, *1967*: Sept., 1128-1131, 1140
  for bacterial endocarditis, *1968*: Sept., 1098
  for Klebsiella pneumonia, *1967*: March, 545
  for pneumococcal pneumonia, *1967*: March, 543
  for postoperative staphylococcal infections, *1966*: May, 798
  for staphylococcal pneumonia, *1967*: March, 544
  toxicity, *1967*: July, 928
Ceporin, *1967*: Sept., 1128
Cerebellopontine angle syndrome, *1968*: July, **789-795**
  aneurysm and, *1968*: July, 792
  astrocytoma and, *1968*: July, 792, 793
  eighth nerve neuroma and, *1968*: July, 789, 791
  intracranial hemangioma and, *1968*: July, 793
Cerebellum, astrocytoma of, cerebellopontine angle syndrome and, *1968*: July, 793
  lesions of, speech disturbances in, *1968*: July, 838-842
Cerebral ischemia, hyperbaric oxygen in, *1967*: Sept., 1311
Cerebral vascular disease, diagnosis, *1967*: Jan., 117
  preventability, *1967*: Jan., **105-111**
  prevention, medical measures, *1967*: Jan., 109
    surgery in, *1967*: Jan., 110, **113-122**
Cerebrospinal fluid, cancer cells in, *1966*: May, 660

Cerebrospinal fluid (*Continued*)
  cultures, in management of infections, *1966*: Sept., 1421
  examination of, in stroke, *1968*: Sept., 1198
Cerebrum, disorders of, chronic renal failure and, *1968*: July, 845-846
  metabolic abnormalities and, *1968*: July, 846
Cervical block, in office, *1968*: Jan., 181
Cervical rib syndrome, *1968*: July, 777
Cervical root, pain and, *1968*: July, 773-776
  herniated disk and, *1968*: July, 775
  spinal cord hypertrophy and, *1968*: July, 775
Cervical root syndrome, *1967*: July, **1027-1034**
  coronary artery disease and, differentiation, *1967*: July, 1027, 1032
Cervix uteri, carcinoma, diagnosis, cytologic, *1966*: May, 652, 663
  mortality, *1966*: May, 624
Chair rest. See under *Rest.*
Charcot-Marie-Tooth disease, *1968*: July, 903
Charcot's joint, synovianalysis in, *1966*: Sept., 1287
Chemical agents, as cancer incitants, *1966*: May, 871
Chemotherapy, of cancer, drugs employed in, *1966*: May, **857-868**
  gastrointestinal, metastatic, *1966*: March, **427-438**
  gastrointestinal effects, *1966*: May, 751
  of breast, *1966*: Sept., 1459, 1463
  of lung, inoperable, *1967*: March, 566
  of ovary, advanced, *1966*: May, 850
  of chronic granulocytic leukemia, *1966*: May, 806
  of Hodgkin's disease, *1966*: May, 826, Nov., 1605
  of multiple myeloma, *1966*: Nov., 1570
Chest, pain in, postoperative, *1968*: Jan., **91-101**
Chiasm, optic, lesions of, pupillary reflexes in, *1968*: July, 877
Chickenpox, encephalitis following, *1967*: May, 711
Childbirth, easy or difficult, psychologic evaluation, *1967*: Nov., 1482
Children, adolescent. See *Adolescents.*
  development, emotional and personality, *1967*: Nov., 1435
  diarrhea in, *1967*: May, 643
  immunization, prophylactic, *1967*: May, **581-586**
  mental health techniques, training in, *1967*: Nov., 1436
  pain relief in, *1968*: Jan., **131-136**
Children (*Continued*)
  poststreptococcal acute glomerulonephritis in, *1966*: July, **1141-1158**
  psychologic problems in, assessment by clinical psychologist, *1967*: Nov., 1482
    principles of training pediatricians in, *1967*: Nov., **1427-1438**
  respiratory infection in, clinical syndromes, *1967*: May, **819-829**
  tuberculosis in, drug resistant, newer and second-line drugs in, *1967*: Sept., **1153-1167**
Chlophedianol hydrochloride in chronic bronchitis, *1967*: Sept., 1176
Chlorambucil, as anticancer agent, *1966*: May, 858, 862
  for Hodgkin's disease, *1966*: Nov., 1606
  for polycythemia vera, *1966*: Nov., 1507
Chloramphenicol, toxicity, *1967*: July, 932
Chlordiazepoxide for alcoholism, *1967*: Sept., 1250
  for pain, *1968*: Jan., 52
Chloride, loss, gastrointestinal, disorders of renal function with, *1966*: July, 1000, 1003
Chlormadinone acetate, *1967*: Sept., 1263
Chloromycetin. See *Chloramphenicol.*
Chloroquine, for rheumatoid arthritis, *1967*: Sept., 1221; *1968*: May, 761
Chloroquine retinopathy, fluorescein angiography of fundus in, *1968*: July, 866
Chlorothiazide for hypertension, *1967*: July, 987
Chlorpromazine, for alcoholism, *1967*: Sept., 1251
  for hypovolemic shock, *1967*: Jan., 94
  for pain, *1968*: Jan., 51
Cholangiography, transhepatic, percutaneous, for cancer diagnosis, *1966*: May, 757
Cholecystectomy in cardiac patient, *1966*: March, **495-500**
Cholecystitis, pain pattern in, *1968*: Jan., 105
Cholecystokinin-pancreozymin, structure, secretion, and action, *1968*: Nov., 1301
Cholera, immunization, for foreign travel, *1967*: May, 843
  influence of age and nutrition on, *1967*: May, 647
  prevention and control, *1967*: May, **625-635**
  vaccines, *1967*: May, 630
Cholestasis, benign, recurrent, familial, *1968*: Nov., 1422
  intrahepatic, *1968*: Nov., 1421
    familial, *1968*: Nov., 1275
Cholesterol, blood, tests for, *1968*: Nov., 1432

Cholesterol (*Continued*)
  control of, dietary, *1968*: Sept., 1251
    drug, *1968*: Sept., 1253-1259
  input and output, *1968*: Sept., 1250
  role, in atherosclerosis, *1967*: Jan., 98
  serum, coronary heart disease and, *1966*: Jan., 231; *1967*: Jan., 126; *1968*: Sept., 1249, 1250
Cholestyramine, for hypercholesterolemia, *1968*: Sept., 1255
Choloxin. See *Dextrothyroxine.*
Chondrocalcinosis, articular, in hyperparathyroidism, *1967*: July, 878
Choreoathetosis, speech disturbances in, *1968*: July, 838-842
Choreoretinitis, fluorescein angiography of fundus in, *1968*: July, 861
Choroid, hemangioma of, fluorescein angiography of fundus in, *1968*: July, 858
  tumor of, metastatic, fluorescein angiography of fundus in, *1968*: July, 864
Choroiditis, fluorescein angiography of fundus in, *1968*: July, 861
Chromophobe adenoma, endocrine glands and, *1968*: July, 830-834
  symptoms and signs of, early, *1968*: July, **827-834**
Chromosomes, alterations, in cancer, *1966*: May, **875-885**
  in benign cells, *1966*: May, 876
Chronic disease, emotional reactions to, *1967*: Nov., **1399-1408**
Chrysotherapy, for rheumatoid arthritis, *1968*: May, **733-738**
  juvenile, *1968*: May, 586
Chylothorax, lymphangiography in, *1967*: Jan., 242, 243
Chyluria, lymphangiography in, *1967*: Jan., 243
Chymotrypsin, as aerosol, *1967*: March, 312
Cigarette smoking, and cancer, *1966*: May, 638, 644, 645
  as coronary risk factor, *1966*: Jan., 241
Cineangiography, coronary, selective, *1967*: July, 942
Circle of Willis, aneurysms of, hemorrhagic stroke and, *1968*: Sept., 1200, 1204
Circumcision, and cancer, *1966*: May, 639
Cirrhosis, biliary, primary autoimmunity and, *1968*: Nov., 1289
  Laennec's, esophageal varices and, *1968*: Nov., 1458
  of liver, cancer and, *1966*: May, 753
    genetic factors in, *1968*: Nov., 1278
    implications of current research in, *1968*: Nov., 1405
    in alcoholics, *1968*: Nov., **1445-1455**
      incidence and susceptibility, *1968*: Nov., 1448

Cirrhosis (*Continued*)
  of liver, in alcoholics, recognition, *1968*: Nov., 1450
      therapy, *1968*: Nov., 1452
Citanest. See *Propitocaine.*
Clicks, systolic, *1966*: Sept., 1213
Climate, rheumatoid arthritis and, *1968*:
Clofibrate (Atromid S), for diabetes with obesity, *1966*: Sept., 1377, 1378
  for hypercholesterolemia, *1968*: Sept., 1256
Clomid. See *Clomiphene.*
Clomiphene, for amenorrhea, *1968*: March, 354
Clot retraction, biomechanics, *1966*: Sept., 1266
Clotting, disturbances, in liver disease, *1966*: March, 544
Cloxacillin, *1967*: Sept., 1112
  in postoperative staphylococcal infections, *1966*: May, 797
  toxic reactions, *1967*: July, 931
Clubbing, in carcinoma of lung, *1967*: July, 1043
  of fingers and toes, hyperthyroidism and, *1968*: March, **393-398**
Coagulation, blood, biochemical defects, *1966*: Sept., **1257-1270**
    defects, treatment, *1967*: Sept., **1241-1247**
    intravascular, anticoagulants in, *1966*: Nov., 1673
      treatment, *1967*: Sept., 1245
Coarctation of aorta. See under *Aorta.*
Cocaine, in office, *1968*: Jan., 178
Coitus, early, and cancer, *1966*: May, 640
Cold, common, *1967*: May, 809
    in children, *1967*: May, 821
    prospects for control, *1967*: May, **765-768**
Cold agglutinins, role, in blood incompatibility, *1966*: Nov., 1645
Colistimethate, toxic reactions, *1967*: July, 932
Colistin, *1967*: Sept., 1128-1131, 1133
Colitis, granulomatous, *1968*: Nov., 1387-1392
  ulcerative, articular manifestations, *1966*: March, 421
    autoimmunity and, *1966*: March, 405; *1968*: Nov., 1291
    colonic and systemic manifestations, *1967*: July, **1011-1013**
    complications, *1968*: Nov., 1390
    diagnosis, *1968*: Nov., 1389
    disaccharidase deficiency and, *1968*: Nov., 1361
    extracolonic manifestations, *1966*: March, **529-534**
    lymphomas simulating, *1966*: May, 750
    pathology, *1968*: Nov., 1388

Colitis (*Continued*)
  ulcerative, prognosis and treatment, *1968*: Nov., 1390
    roentgen examination, *1968*: Nov., 1390
    sigmoidoscopic examination, *1968*: Nov., 1389
    uncommon abnormalities of blood with, *1966*: March, 535
    vs. granulomatous, *1968*: Nov., 1387-1392
    with ankylosing spondylitis, *1968*: May, 508, 512
    with arthritis, *1968*: May, 507-509
    with erythema nodosum, *1968*: May, 508
    with polyarthritis, *1968*: May, 508
Collagen diseases. See *Connective tissue disorders.*
Collecting duct of kidney, *1966*: July, 934
Colon, carcinoma, diagnosis, cytologic, *1966*: May, 659
    mortality, *1966*: May, 617
    radiation therapy for, pain, *1968*: Jan., 206
  Crohn's disease. See *Colitis, granulomatous.*
  cytological examination, *1968*: Nov., 1325
  diverticula, Marfan's syndrome and, *1968*: Nov., 1277
  irritable, *1966*: March, **591-595**
  polyposis, familial, *1966*: March, **379-392**
    inheritance, *1968*: Nov., 1274
Coly-Mycin. See *Colistin.*
Coma, hepatic, management, *1968*: Nov., **1475-1481**. See also *Hepatic coma.*
  myxedema, *1968*: March, 445
    thyroid hormones in, *1966*: Sept., 1397
Common cold. See *Cold, common.*
Community services of state hospitals, *1967*: Nov., 1470
Compatibility tests, appraisal, *1966*: Nov., **1643-1652**
Compazine. See *Prochlorperazine.*
Complement system, rheumatoid arthritis inflammation and, *1968*: May, 628-629
Congo red test, for amyloid, *1968*: May, 650
Conjunctiva, topical analgesia, *1968*: Jan., 178
Conjunctivitis, with arthritis, *1968*: May, 504
Connective tissue, changes, rheumatoid arthritis and, *1968*: May, 598-600
  disorders, autoimmune aspects, *1966*: March, 402
  chronic biologic false-positive test for syphilis in, *1966*: Sept., **1271-1279**
Connective tissue (*Continued*)
  gastrointestinal manifestations, *1966*: March, 417, 508
  renal manifestations, *1966*: March, 508
Contraception, oral, *1967*: Sept., **1261-1275**
    amenorrhea and, *1968*: March, 343
    complications, *1967*: Sept., 1269, 1270
    varicose veins and, *1968*: Sept., 1085
Conversion reactions, internist's role, *1967*: Nov., 1418
Convulsions. See *Seizures, convulsive.*
Coombs antiglobulin test in diagnosis of anemias, *1966*: Nov., 1699
Copper, metabolism of, Wilson's disease and, *1968*: July, **989-1001**
Cor pulmonale, classification, physiological, *1966*: Jan., **37-49**
  diagnostic features, *1966*: Jan., 38, 39
Cordotomy, percutaneous, techniques and results, *1968*: Jan., **189-201**
Cornea, topical analgesia, *1968*: Jan., 178
Coronary arteriography, *1966*: Jan., 138
Coronary artery disease, atherosclerotic, anticoagulant therapy, *1967*: Jan., 130
    dietary treatment, *1967*: Jan., 126
  cervical root syndrome and, differentiation, *1967*: July, 1027, 1032
  manifestations, unusual, *1967*: July, **941-947**
  pathogenesis, *1967*: Jan., **123-137**
  prophylaxis, *1967*: Jan., 125
  risk factors, their impact and their therapy in prevention, *1966*: Jan., **229-253**
  serum lipid levels and, *1968*: Sept., **1249-1260**
Coronary care unit, myocardial infarction and, *1968*: Sept., 1065
Coronary cineangiography, selective, *1967*: July, 942
Coronary insufficiency, serum enzymes in, *1966*: Jan., 181
Corpus luteum, steroid production by, *1967*: July, 907, 910
Corticosteroids, as aerosols, *1967*: March, 313
  as anticancer agents, *1966*: May, 860, 866
  erythropoiesis and, *1968*: March, 237
  for acute granulocytic leukemia, dangers, *1966*: Nov., **1653-1668**
  for autoimmune diseases, *1966*: March, 407
  for cancer, gastrointestinal bleeding and, *1966*: May, 748
    of breast, *1966*: Sept., 1462
  for diffuse interstitial pulmonary fibrosis, *1967*: March, 447
  for herpes zoster, *1968*: Jan., 115

Corticosteroids (*Continued*)
  for Hodgkin's disease, *1966*: May, 828, Nov., 1607
  for inoperable lung cancer, *1967*: March, 567
  for multiple myeloma, *1966*: Nov., 1574
  for postoperative infections, *1966*: May, 800
  for rheumatoid arthritis, *1967*: Sept., 1214; *1968*: May, 693, **739-746**
    juvenile, *1968*: May, 585
  for sarcoidosis, *1967*: March, 497
  for status asthmaticus, *1967*: March, 380
  for tuberculosis, *1966*: Sept., 1440
  leukopoiesis and, *1968*: March, 240
  neurologic side effects, *1968*: July, 850
  newer, for nonviral encephalitis, *1967*: Sept., **1189-1202**
    possible mechanisms, *1967*: Sept., 1197
    vs. ACTH, *1967*: Sept., 1197
Corticotropin, erythropoiesis and, *1968*: March, 237
  secretion of, excess, *1968*: March, 359
  tumors secreting, *1968*: March, 323
    treatment, *1968*: March, 324
Cortisol, for hypertension due to adrenal hyperplasia, *1968*: Sept., 1229
  insulin antagonism and, *1968*: March, 254
Cortisone. See *Corticosteroids.*
Cortisone suppression test, hyperparathyroidism and, *1968*: March, 458
Costoclavicular syndrome, *1968*: July, 777
Cough, control, in chronic obstructive lung disease, *1967*: March, 355
C-Quens, *1967*: Sept., 1263
Cranial nerve(s), chronic renal failure and, *1968*: July, 847
  eighth, neuroma of, cerebellopontine angle syndrome and, *1968*: July, 789, 791
  lesions of, at cerebellopontine angle, *1968*: July, **789-795**
Creatine, metabolism of, myopathy and, *1968*: March, 247
Creatinuria, myopathy and, *1968*: March, 247
Crigler-Najjar syndrome, *1968*: Nov., 1420
  inheritance, *1968*: Nov., 1275
Criminal, psychiatry and, *1967*: Nov., 1473
Crohn's disease. See *Colitis, granulomatous.*
Crooke cell, pathophysiology, *1968*: March, 320
Croup, spasmodic, *1967*: May, 823
Cryptococcosis, pulmonary, *1967*: March, **519-527**
Crystals in synovial fluid, *1966*: Sept., 1286
Culdoscopy, in amenorrhea, *1968*: March, 351
Cultures, role, in management of infections, *1966*: Sept., **1420-1429**
Cushing's syndrome, adrenocortical tumors and, *1968*: March, 320
  amenorrhea and, *1968*: March, 344
  clinical pattern and pathological findings, *1968*: March, **313-326**
  Crooke cell and, *1968*: March, 320
  diagnosis, *1968*: March, 313; Sept., 1217, 1223
  ectopic corticotropin-secreting tumor and, *1968*: March, 323
  erythropoiesis in, *1968*: March, 238
  etiology and diagnosis, *1967*: Jan., 20, July, **883-901**
  hypophyseal tumors and, *1968*: March, 320
  in lung cancer, treatment, *1967*: March, 570
  in nonendocrine cancer, *1966*: May, 770
  muscle weakness and, *1968*: March, 245
  pancreatic islet cell tumors and, *1968*: March, 304
  treatment, *1968*: March, 324
  without tumor, *1968*: March, 323
Cyanocobalamin. See *Vitamin* B_{12}.
Cyclazocine, analgesic properties, *1968*: Jan., 39
Cyclophosphamide, as anticancer agent, *1966*: May, 858, 862
  for gastrointestinal cancer, *1966*: March, 430
  for Hodgkin's disease, *1966*: May, 827, Nov., 1606
  for multiple myeloma, *1966*: Nov., 1573
  for polycythemia vera, *1966*: Nov., 1508
  for rheumatoid arthritis, *1967*: Sept., 1221; *1968*: May, 696, 750, 751
Cycloserine, for drug-resistant tuberculosis in children, *1967*: Sept., 1156, 1162, 1163
  for tuberculosis, *1966*: Sept., 1437, 1439
    of kidney, *1966*: July, 1138
Cystic fibrosis, of pancreas, inheritance, *1968*: Nov., 1278
  pancreatic insufficiency in, *1966*: March, 452
Cysts, bone, in hyperparathyroidism, *1967*: July, 878
  multiple, of kidney, congenital, pathogenesis, diagnosis and treatment, *1966*: July, **1101-1117**
  renal, radiograms in, *1967*: Jan., 61, 63

Cytellin. See *Sitosterol.*
Cytology, exfoliative, in gastrointestinal disease, *1968*: Nov., **1315-1328**
  diagnostic criteria, *1968*: Nov., 1316-1319
  techniques, *1968*: Nov., 1315
 liver, for cancer diagnosis, *1966*: May, 756
 methods, in diagnosis of cancer, *1966*: May, **651-666**
  of non-neoplastic disease, *1966*: May, 662
  recent technical modifications, *1966*: May, 662
 pancreas, for cancer diagnosis, *1966*: May, 758
Cytoplasmic inclusion granules in synovial fluid, *1966*: Sept., 1285
Cytosine as anticancer agent, *1966*: May, 859, 864
Cytotoxic drugs for autoimmune diseases, *1966*: March, 408
 for rheumatoid arthritis, *1968*: May, 696, **747-757**
Cytoxan. See *Cyclophosphamide.*

Darcil, *1967*: Sept., 1108
DBI. See *Phenformin.*
DCI. See *Dichloroisoproterenol.*
Deafness, retrocochlear lesion and, *1968*: July, 790
Decompression sickness, *1967*: Sept., 1306, 1307
 hyperbaric oxygen in, *1967*: Sept., 1308
Dehydrogenases, serum, activity of, effects of vitamin B_{12} therapy on, *1966*: Nov., 1628, 1631
  in myocardial and other organ injury, *1966*: Jan., **193-209**
  in pulmonary embolism, *1967*: Jan., 176
Dejerine-Sottas disease, *1968*: July, 903
Delalutin in endometrial cancer, *1966*: May, 836
Deltoin. See *Methetoin.*
Demecolcin in chronic myeloblastic leukemia, *1966*: May, 807
Demerol. See *Meperidine hydrochloride.*
Dependency in chronic illness, *1967*: Nov., 1404
Depressions, drug therapy, *1967*: Nov., 1460
 in aged persons, *1967*: Nov., 1519
 in chronic illness, *1967*: Nov., 1403
 internist's role, *1967*: Nov., 1420
 treatment, general principles, *1967*: Nov., 1462
Dermatitis, contact, from drugs, *1967*: July, 1087
 exfoliative, drug-induced, *1967*: July, 1076, 1081
Deserpidine for hypertension, *1967*: Jan., 31
Desoxyn. See *Methamphetamine.*
Detergent aerosols, *1967*: March, 315
Deteriorative processes, appraisal, by clinical psychologist, *1967*: Nov., 1480
Dexamethasone, for rheumatoid arthritis, *1967*: Sept., 1215; *1968*: May, 743
 test for Cushing's syndrome, *1967*: July, 892, 899
Dexedrine. See *Dextroamphetamine.*
Dextran, for hypovolemic shock, *1967*: Jan., 91, 92
 low molecular weight, for shock of myocardial infarction, *1967*: Jan., 71, 74, 78
  pharmacology and clinical uses, *1967*: Sept., **1285-1299**
Dextroamphetamine (Dexedrine), for narcolepsy, *1968*: July, 783
Dextrothyroxine (Choloxin), clinical uses, *1966*: Sept., 1393
 for hypercholesterolemia, *1968*: Sept., 1254
Diabetes, chronic pancreatitis and, *1968*:
Diabetes insipidus, causes, *1968*: March, 384
Diabetes mellitus, acetohexamide in, *1966*: Sept., 1376, 1378
 Addison's disease and, *1968*: March, 336
 as coronary risk factor, *1966*: Jan., 237
 coma of. See *Coma, diabetic.*
 control of, during acute complications, *1966*: Sept., 1382
  standards, *1966*: Sept., **1371-1383**
 dietary management, *1966*: Sept., 1379
 fluorescein angiography of fundus in, *1968*: July, 858
 in adrenocortical disease, *1967*: July, 887
 in pancreatic disease, *1966*: March, 454
 insulin treatment, *1966*: Sept., 1379
 long-term, without vascular disease, *1966*: Sept., **1385-1391**
 neuropathy and, *1966*: March, **565-568**; *1968*: July, 905
 obesity and, *1966*: Sept., 1372
 oral hypoglycemic compounds in, *1966*: Sept., 1375, 1378
 orthostatic hypotension and, *1968*: July, 812
 parietal cell antibody and, *1968*: Nov., 1286
 phenformin for, *1966*: Sept., 1376, 1378

Diabetes mellitus (*Continued*)
  polyneuropathy and, *1968*: Jan., 112
  pregnancy and, *1968*: March, 253
  tolbutamide for, *1966*: Sept., 1376, 1378
Diabinese. See *Chlorpropamide.*
Diagnosis, medical, comprehensive, for internist, *1967*: Nov., **1381-1397**
  for chronic renal failure, *1966:* July, 1185
Dialysis, for congestive heart failure, *1968:* Sept., 1176
  in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1149
  neurologic complications, *1968*: July, 849
Diamox. See *Acetazolamide.*
Diarrhea, in children, *1967*: May, 643
  in thyroid disease, *1966*: March, 583
  in Zollinger-Ellison syndrome, *1966*: March, 476
  infectious, *1968*: Nov., 1361
  Salmonella, *1967*: May, 647
  tropical, cutaneous melanosis with, *1966*: March, 351
  viral, *1967*: May, 637
  weanling, *1967*: May, 643
Diarrheal diseases, current problems, *1967*: May, **609-615**
Diazepam, for pain, *1968*: Jan., 52
  for recurrent convulsions, *1968*: July, **977-987**
  for status epilepticus, *1968*: July, 968
Dibenamine, blocking action, *1968*: Sept., 1011
Dibenzyline. See *Phenoxybenzamine.*
  for hypovolemic shock, *1967*: Jan., 93
Dichloroisoproterenol (DCI), blocking action, *1968*: Sept., 1011
Dicloxacillin, *1967*: Sept., 1115
  in postoperative staphylococcal infections, *1966*: May, 797
Diet, after myocardial infarction, *1968*: Sept., 1066
  as coronary risk factor, *1966*: Jan., 239
  in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1148
  in prevention of atherosclerosis, *1967*: Jan., 98
  in refractory heart failure, *1968*: Sept., 1165
  low-cholesterol, *1968*: Sept., 1251
Diethylstilbestrol. See *Estrogens.*
Diffusion, pulmonary, *1967*: March, **427-438**
Digestive tract, cancer, mortality, *1966*: May, 616
Digitalis, for alcoholic myocardiopathy, *1968*: Sept., 1187
Digitalis (*Continued*)
  for hypovolemic shock, *1967*: Jan., 94
  for refractory heart failure, *1968*: Sept., 1164
  intoxication, gastrointestinal manifestations, *1966*: March, **501-506**
DiGuglielmo syndrome, *1966*: Nov., 1552; *1967*: July, 1055
  leukoerythroblastosis in, *1966*: May, 788
Dilantin. See *Diphenylhydantoin.*
Dimesthisterone, *1967*: Sept., 1263
Dimocillin-RT, *1967*: Sept., 1109
Diphenylhydantoin (Dilantin), for cardiac arrhythmias, *1967*: Sept., 1230
  for status epilepticus, *1968*: July, 968
  for trigeminal neuralgia, *1968*: Jan., 112; *1968*: July, 798
Disaccharidases, *1968*: Nov., 1356
  deficiency, *1968*: Nov., **1355-1365**
    clinical disorders associated with, *1968*: Nov., 1357-1362
Disaccharides, absorption, *1968*: Nov., 1355
Disease(s), chronic, emotional reactions to, *1967*: Nov., **1399-1408**
    management, *1967*: Nov., 1406
    family relationships in, *1967*: Nov., 1405
  role of patient, and what the doctor can do about it, *1967*: Nov., **1507-1514**
  systemic, gastrointestinal tract and, symposium on, *1966*: March, **347-602**
  unusual manifestations, symposium on, *1967*: July, **857-1091**
Disks, intervertebral, degeneration of, low back pain and, *1968*: Jan., 62
    herniated, cervical root pain and, *1968*: July, 775
Disulfiram for alcoholism, *1967*: Sept., 1256
Dithiazinine iodine for pinworm infestation, *1967*: Sept., 1207
Diuretics, for alcoholic myocardiopathy, *1968*: Sept., 1187
  for hypertension, *1966*: Jan., 297; *1967*: Jan., 30; *1968*: Sept., 1231
  for refractory heart failure, *1968*: Sept., 1166
  furosemide and ethacrynic acid as, *1967*: Sept., **1277-1283**
  renal complications, *1966*: Jan., 266
Diuril. See *Chlorothiazide.*
DNA-RBC test, for antinuclear factors, *1968*: May, 561
Doctor. See *Physician.*
Dolvex, *1967*: Sept., 1207
Doriden. See *Glutethimide.*
Dornase, pancreatic, as aerosol, *1967*: March, 311

Drowsiness, diurnal, *1968*: July, 781
Drugs, anticancer, selection, for inclusion in Memorial Hospital formulary, *1966*: May, **857-868**
  antidepression, *1967*: Nov., 1460
  antifungal, and their indications, *1967*: Sept., **1181-1188**
  antimicrobic, newer, for gram-negative infections, *1967*: Sept., **1127-1152**
    toxic reactions, *1967*: July, **925-940**
  antirheumatic, *1967*: Sept., **1213-1222**
  antituberculosis, second-line, new, *1967*: Sept., **1153-1167**
  effects, study by electron microscope, *1966*: May, 896
  eruption, fixed, *1967*: July, 1076, 1082
  immunosuppressive, for rheumatoid arthritis, *1967*: Sept., 1220
    for status asthmaticus, *1967*: March, 380
  newer, efficacy of, symposium on, *1967*: Sept., **1105-1343**
    for pinworm infestation, *1967*: Sept., **1203-1211**
  pancreatitis due to, *1966*: March, 453
  photosensitivity to, *1967*: July, 1077, 1086
  psychotherapeutic, use, *1967*: Nov., **1453-1466**
  reactions, cutaneous, *1967*: July, **1073-1088**
    fever in, *1966*: Jan., 219
    oral manifestations, *1966*: March, 368
    vs. juvenile rheumatoid arthritis of polyarticular onset, *1968*: May, 578
  renal complications, *1966*: Jan., 265
  tests with, as aid to cardiac auscultation, *1966*: Jan., 73, 86
Dubin-Johnson syndrome, *1968*: Nov., 1422
  inheritance, *1968*: Nov., 1276
Duct, collecting, of kidney, *1966*: July, 934
Ductus arteriosus, patent, *Jan.*, 1967
    in adult, clinical picture, *1966*: Jan., 28
    phonocardiogram in, *1966*: Jan., 106
      after amyl nitrite, *1966*: Jan., 82
Duodenum, cytological examination, *1968*: Nov., 1323
  disorders of, pain patterns in, *1968*: Jan., 107
Dura, neuroanatomy, *1968*: Jan., 187
Dusts, organic, pulmonary granulomatoses due to, *1967*: March, **459-482**
Dymelor. See *Acetohexamide.*
Dyrenium. See *Triamterine*
Dysarthria, neurologic disease and, *1968*: July, **835-844**
  patterns, *1968*: July, 841-844
Dyscrasias, blood, oral manifestations, *1966*: March, 367
Dysentery, amebic, current problems, *1967*: May, **609-615**
  bacillary, malnutrition and, *1967*: May, 649
  viral, *1967*: May, 637
Dysinsulinism, *1966*: March, 455
Dysmenorrhea, oral contraceptive drugs and, *1967*: Sept., 1269, 1272
  psychologic aspects, *1967*: Nov., 1377
Dyspnea, due to heart and to lung disease, use of pulmonary function tests in separating, *1966*: Jan., 153
  in diffuse interstitial pulmonary fibrosis, *1967*: March, 440
  in farmer's lung, *1967*: March, 460, 479
  nature, *1966*: Jan., 141
    in heart disease due to lung function alterations, *1966*: Jan., 151
Dysrhythmia, after myocardial infarction, *1968*: Sept., 1067
Dystonia, speech disturbances in, *1968*: July, 838-842
Dystrophy, muscular, oculopharyngeal, inheritance, *1968*: Nov., 1275
  sympathetic, post-traumatic, *1968*: Jan., 152
    reflex, *1968*: Jan., 127
Dysventilation syndromes with heart failure, diagnosis, *1966*: Jan., 39, 44

EAR, pain, in rheumatoid arthritis, *1967*: July, 1020
Ectopic beats, usefulness in cardiac diagnosis and prognosis, *1966*: Jan., 51-64
Edecrin. See *Ethacrynic acid.*
Edema, angioneurotic, hereditary, *1966*: March, 399
  in adrenocortical disease, *1967*: July, 887
  in gluten enteropathy, *1966*: March, 522
  in Graves' disease, *1967*: July, 922
  pulmonary, after myocardial infarction, *1968*: Sept., 1072
Effusions, cancer cells in, *1966*: May, 660
Eisenmenger syndrome, *1966*: Jan., 152
Elbow, in rheumatoid arthritis, *1968*: May, 496
    surgery, *1968*: May, 724
Elderly. See *Aged persons.*
Electrocardiography, ectopic beats, *1966*: Jan., 51-64
  findings indicating coronary risk, *1966*: Jan., 243
  in atrial septal defects, *1967*: July, 953
  in pulmonary embolism, *1967*: Jan., 182

Electrocardiography (*Continued*)
  postextrasystolic beats, *1966*: Jan., 64-70
  supernormal conduction, *1966*: Jan., 61
  supernormal phase of recovery, *1966*: Jan., 61
  vulnerable phase, extrasystoles in, *1966*: Jan., 60
Electroencephalogram, abnormalities in, techniques for activating, *1968*: July, 952-953
  artifacts in, biologic, *1968*: July, 941
  in chronic renal failure, *1968*: July, 846-847
  localization of seizure origin by, *1968*: July, 953-957
  of fetus, *1968*: July, 946
  patterns in, clinical significance, *1968*: July, **933-940**, 949-951
  positive spikes in, 14 and 6 per second, *1968*: July, 933-934
  small sharp spikes in, *1968*: July, 934-939
Electroencephalography, extracerebral, *1968*: July, **941-948**
  in evaluation of seizures, *1968*: July, **949-957**
Electrolytes, fluids and, disturbances in cancer, *1966*: May, **711-732**
    effects on heart, *1966*: May, 742
    in renal failure, *1966*: July, 1178
  metabolism, *1966*: May, 719
Electromyography, *1968*: July, 943
Electron microscopy, in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1146
  muscle disease and, *1968*: July, **909-931**. See also under *Muscles*.
  of cancer cells, *1966*: May, **887-900**
  of normal and diseased blood vessels, *1967*: Jan., **139-150**
Electronystagmography, *1968*: July, 944
Electro-oculogram, *1968*: July, 945
Electroretinography, *1968*: July, 944, 945
Embolectomy, pulmonary, case for, *1967*: Jan., **185-191**
  technique, *1967*: Jan., 188
Embolism, air, and its treatment, *1967*: Sept., 1306, 1308
  arterial, systemic, in coronary artery disease, *1967*: July, 945
  fat, low molecular weight dextran in, *1967*: Sept., 1294
  pulmonary, angiocardiography in, *1966*: Jan., 138
    embolectomy for, *1967*: Jan., **185-191**
    fever in, *1966*: Jan., 216
    laboratory diagnosis, limitations, *1967*: Jan., **175-184**
    postoperative chest pain and, *1968*: Jan., 95

Embolism (*Continued*)
  pulmonary, serum enzymes in, *1966*: Jan., 185, 203
    with heart disease, *1966*: Jan., 40, 43
  renal, arteriogram in, *1967*: Jan., 58, 59
Embolus, prosthetic heart valves and, *1968*: Sept., 1134
  saddle, *1967*: Jan., 211
Emotional development of child, *1967*: Nov., 1435
Emotional disturbances, appraisal, by clinical psychologist, *1967*: Nov., 1480
  in adolescents, complex, *1967*: Nov., 1442
  in aged persons, management, *1967*: Nov., **1515-1527**
  in chronic physical illness, *1967*: Nov., **1399-1408**
    management, *1967*: Nov., 1406
Emphysema, asthma and, relationship, *1967*: March, 275
  bronchitis and, clinical manifestations and their physiologic significance, *1967*: March, **283-292**
    relationship, *1967*: March, 275
  etiology, *1967*: March, 276
  heart, *1966*: Jan., 45
  obstructive, diffuse, unusual manifestations, *1967*: July, **1045-1049**
  pathology and pathogenesis, *1967*: March, **269-281**
  pulmonary, peptic ulcer with, *1966*: March, **479-486**
    management, *1966*: March, 481
Encephalitis, California group, *1967*: May, 668
  Eastern and Western, *1967*: May, 661
  measles, corticosteroids in, *1967*: Sept., 1190
  nonviral, newer steroids in, *1967*: Sept., **1189-1202**
    possible mechanisms, *1967*: Sept., 1193
  postinfectious, *1967*: May, **701-717**
    corticosteroids or ACTH in, *1967*: Sept., 1191, 1198
  postvaccinal, *1967*: May, **701-717**
  St. Louis, *1967*: May, 665
  vector-borne, in Middle Atlantic states, *1967*: May, **661-671**
Encephalomyelitis, acute, disseminated, after nonspecific upper respiratory disease, corticosteroids in, *1967*: Sept., 1192
  cryptogenic, corticotropin in, *1967*: Sept., 1198
  postrabies vaccine, corticosteroids in, *1967*: Sept., 1191, 1198
Encephalopathy, hepatic. See *Hepatic coma*.
  thyrotoxic, acute, *1967*: July, 922

Endocarditis, bacterial, causes, *1968*: Sept., 1091, 1092
    changing patterns, *1968*: Sept., **1091-1101**
    complications, *1968*: Sept., 1099
    diagnosis, *1968*: Sept., 1094
    fever in, *1966*: Jan., 218
    negative blood cultures in, a decade's experience, *1966*: Jan., **159-170**
    penicillins for, *1967*: Sept., 1117
    prevention, *1968*: Sept., 1096, 1097
    rare types, *1968*: Sept., 1093
    renal lesions, *1966*: Jan., 263
    treatment, *1968*: Sept., 1097
  malignant, vs. cancer of heart, *1966*: May, 744
  prosthetic heart valves and, *1968*: Sept., 1136
  staphylococcal, penicillins in, *1967*: Sept., 1116
  thrombotic, nonbacterial, *1966*: May, 741
Endocardium, tumors, metastatic, *1966*: May, 736
Endocrine glands. See also names of glands.
  chromophobe adenoma and, *1968*: July, 830-834
  diseases, secondary hypertension and, *1968*: Sept., 1214
  disorders, symposium on, *1968*: March, **229-472**
  hematopoiesis and, *1968*: March, **231-241**
  functions, pregnancy and, *1968*: March, **253-262**
Endocrine syndromes associated with nonendocrine neoplasms, *1966*: May, **763-778**
Endocrine therapy, in cancer of ovary, advanced, *1966*: May, 852
Endometrium, biopsy of, in amenorrhea, *1968*: March, 350
  cancer, diagnosis, cytologic, *1966*: May, 653
    etiology, diagnosis and prognosis, *1966*: May, 828
    management, *1966*: May, **828-844**
Energizers, *1967*: Nov., 1460
Enovid, *1967*: Sept., 1263
Enteric infections, current problems, *1967*: May, **609-615**
  incidence and control, influence of age and nutrition on, *1967*: May, **643-652**
  preventive measures, *1967*: May, 651
Enteric organisms, gram-negative, aerobic, postoperative infections due to, treatment, *1966*: May, 799
Enteritis, regional, *1968*: Nov., 1392-1395
    articular manifestations, *1966*: March, 421
Enteritis (*Continued*)
  regional, disaccharidase deficiency and, *1968*: Nov., 1361
    lymphomas simulating, *1966*: May, 750
  viral, *1967*: May, 637
    with ankylosing spondylitis, *1968*: May, 508, 512
Entero-arthropathy, *1966*: March, **417-425**
Enterococcal infections, postoperative, in cancer patients, treatment, *1966*: May, 798
Enteropathy, gluten, systemic manifestations, *1966*: March, **515-527**
    cutaneous melanosis with, *1966*: March, 350
Enterovirus infections of central nervous system, *1967*: May, **681-692**
Enteroviruses in gastrointestinal diseases, *1967*: May, 638
Environmental cancer research, studies in, *1966*: May, **631-650**
Enzymes, congenital deficiencies, *1968*: Nov., 1276
  in blood coagulation, *1966*: Sept., 1259
  lysosomal, rheumatoid arthritis and, *1968*: May, 600-601
  pancreatic, in cancer diagnosis, *1966*: May, 758
  proteolytic, in chronic bronchitis, *1967*: Sept., 1178
  serum, in myocardial infarction and related cardiovascular conditions, *1966*: Jan., **171-191**
    in pulmonary embolism, *1967*: Jan., 176
  studies in gastric juice for cancer, *1966*: May, 754
Eosinophilia in ulcerative colitis, *1966*: March, 539
Ephedrine, for orthostatic hypotension, *1968*: July, 814
  for shock, *1968*: Sept., 1085
Epidermal necrolysis, toxic, *1967*: July, 1076, 1080
Epidural space, anatomy, *1968*: Jan., 209
Epilepsy, electroencephalographic patterns in, *1968*: July, 933-934
  treatment, general rules, *1968*: July, 973-974
  vs. orthostatic hypotension, *1968*: July, 811
Epinephrine, as aerosol, *1967*: March, 310
  for status asthmaticus, *1967*: March, 380
  vasopressor effects, *1967*: July, 982
Epsilon-aminocaproic acid, in fibrinolysis, *1967*: July, 1067, Sept., 1245
  pharmacology, *1966*: Nov., 1669
  treatment with, complications, *1966*: Nov., **1669-1678**

Epulis, in hyperparathyroidism, *1967*: July, 877
Equanil. See *Meprobamate.*
Ergotamine, blocking action, *1968*: Sept., 1011
Erysipelothrix infections of animals, rheumatoid arthritis and, *1968*: May, 667-669
Erythema multiforme, oral lesions, *1966*: March, 364
  multiforme-like lesions, drug-induced, *1967*: July, 1076, 1077
  nodosum, *1967*: March, 486
    with ulcerative colitis, *1968*: May, 508
  nodosum-like lesions, drug-induced, *1967*: July, 1076, 1079
Erythrocytes, indices, in anemias, *1966*: Nov., 1690
  in rheumatoid arthritis, sedimentation rate, *1968*: May, 543
    survival, *1968*: May, 528
Erythroid-myeloid ratio, *1966*: Nov., 1697
Erythrokinetics, tests used in, *1966*: Nov., 1696
Erythroleukemia, *1967*: July, 1055
Erythromycin, in pneumococcal pneumonia, *1967*: March, 542
  toxic reactions, *1967*: July, 929
Erythropoiesis, endocrine effects on, *1968*: March, 232-238
Escherichia coli infections, ampicillin in, *1967*: Sept., 1138
  cephalothin in, *1967*: Sept., 1142
Esophagoscopy, emergency, in bleeding esophageal varices, *1968*: Nov., 1460
Esophagus, carcinoma, diagnosis, cytologic, *1966*: May, 659
    newer techniques, *1966*: May, 754
  cytological examination, *1968*: Nov., 1319
  disease(s), implications of current research in, *1968*: Nov., 1269
  varices, bleeding, diagnosis and treatment, *1968*: Nov., **1457-1474**
    prophylactic portacaval anastomosis and, *1968*: Nov., 1470
Estrogens, as anticancer agents, *1966*: May, 859. 865
  erythropoiesis and, *1968*: March, 233, 234
  for carcinoma of breast, *1966*: Sept., 1461
  for hypercholesterolemia, *1968*: Sept., 1259
  for hypothalamic amenorrhea, *1968*: March, 340
  for ovarian failure, *1968*: March, 346
  insulin antagonism and, *1968*: March, 254
  levels, and skin changes, *1965*: May, 556
Estrogen-progesterone test, in amenorrhea, *1968*: March, 349
Ethacrynic acid (Edecrin), clinical use, *1967*: Sept., **1277-1283**
  for hypertension, *1968*: Sept., 1232
  for refractory heart failure, *1968*: Sept., 1171
Ethambutol in drug-resistant tuberculosis in children, *1967*: Sept., 1159, 1162, 1163
Ethchlorvynol, for pain, *1968*: Jan., 49
Ethinamate, for pain, *1968*: Jan., 49
Ethionamide for tuberculosis, *1966*: Sept., 1436, 1438
  drug-resistant, in children, *1967*: Sept., 1158, 1162, 1163
Ethyl alcohol, for trigeminal neuralgia, *1968*: July, 799
Ethyl carbamate. See *Urethane.*
Ethynodiol acetate, *1967*: Sept., 1263
Ethynylestradiol, *1967*: Sept., 1263
Etiocholanolone fever, *1966*: March, 372
Euglobulin lysis time, test for, *1967*: July, 1067
Euthyroidism vs. hyperthyroidism, thyroid hormones in differentiation, *1966*: Sept., 1400
Eutonyl for hypertension, *1967*: Jan., 34
Exercise, adrenergic receptor blockers and, *1968*: Sept., 1043
  in chronic obstructive lung disease, *1967*: March, 357
  lack of, as coronary risk factor, *1966*: Jan., 239
Exertional headache, benign, *1968*: July, **801-808**
Exophthalmic goiter, thyroid hormones in *1966*: Sept., 1398
  unusual manifestations, *1967*: July, **915-924**
Exophthalmos, progressive, transantral orbital decompression for, *1968*: March, **399-407**
Extracorporeal circulation, use of low molecular weight dextran in, *1967*: Sept., 1292
Extra-sounds, cardiac, drugs in differential diagnosis, *1966*: Jan., 86
Extrasystoles, usefulness, in cardiac diagnosis and prognosis, *1966*: Jan., **51-71**
Extremity(ies), local analgesia of, in office, *1968*: Jan., 180
  occlusive disease, arteriosclerotic, surgery in, *1967*: Jan., 220, 224
  lower, venous diseases, phlebography in, *1967*: Jan., **161-174**
Eye(s), fundus of, fluorescein angiography, *1968*: July, **853-869**
  lesions, in Graves' disease, *1967*: July, 919

Eye(s) (*Continued*)
  lesions, in hyperparathyroidism, *1967*: July, 876
    in rheumatoid arthritis, *1967*: July, 1020
    in ulcerative colitis, *1967*: July, 1012
  tumor metastases to, radiation therapy for pain, *1968*: Jan., 206

FACIAL nerve, cerebellopontine angle lesions and, *1968*: July, 789
Fallopian tube, carcinoma, diagnosis, cytologic, *1966*: May, 653
Family history, rheumatoid arthritis and, *1968*: May, 489-490
Family relationships in chronic illness, *1967*: Nov., 1405
Farmer's lung, *1967*: March, **459-482**
Fasting, as test for hypoglycemia, *1968*: March, 284
Fat embolism, low molecular weight dextran in, *1967*: Sept., 1294
Fats, absorption, normal, *1968*: Nov., 1342
    studies, *1968*: Nov., 1350
Fear, cardiovascular response to, adrenergic receptor blockers and, *1968*: Sept., 1043
  in adolescents, *1967*: Nov., 1450
  in chronic illness, *1967*: Nov., 1400
Febrile convulsions, medical treatment for, *1968*: July, 967
Feet. See *Foot.*
Felty's syndrome, *1968*: May, 529
Femur, head, aseptic necrosis, in sickle cell anemia, *1966*: Nov., 1526
Fertility, effect of oral contraceptive drugs on, *1967*: Sept., 1271
Fetus, dead, with bleeding, antifibrinolytic therapy, *1967*: July, 1065, 1068
Fever, evaluation, for therapy of bacterial endocarditis, *1966*: Jan., 164
  in cancer of liver, *1966*: May, 753
  in heart disease, *1966*: Jan., **211-228**
  in liver disease, *1967*: July, 1005
  juvenile rheumatoid arthritis and, *1968*: May, 570, 575, 577
  obscure, in hypernephroma, *1966*: July, 1073
Fibrillation, atrial, electrical conversion in, *1966*: Jan., **117-125**
    propanolol for, *1968*: Sept., 1020
  ventricular, primary, after myocardial infarction, *1968*: Sept., 1064
Fibrinogen, preparations, in coagulation defects, *1967*: Sept., 1243
Fibrinogenolysis, treatment, *1967*: Sept., 1245
Fibrinolysis, *1967*: July, **1061-1072**
  bleeding due to, *1967*: July, 1064, 1065
Fibrinolysis (*Continued*)
  inhibition by aminocaproic acid, complications, *1966*: Nov., **1669-1678**
  treatment, *1967*: July, 1067, Sept., 1244
Fibrosis, cystic, of pancreas, inheritance, *1968*: Nov., 1278
    pancreatic insufficiency in, *1966*: March, 452
  pulmonary, interstitial, diffuse, *1967*: March, **439-451**
  retroperitoneal, *1966*: July, **1091-1099**
Fingers, clubbing of, hyperthyroidism and, *1968*: March, **393-398**
  paresthesia in, *1968*: July, 774
    thoracic outlet syndromes and, *1968*: July, 777
Fistula(s), aortic, *1967*: Jan., 196
  aortoenteric, *1967*: Jan., 212
  aortovenous, *1967*: Jan., 213
  arteriovenous, angiocardiography in, *1966*: Jan., 137
    of kidney, arteriogram in, *1967*: Jan., 64
    phonocardiogram in, *1966*: Jan., 104
    renal, hypernephroma as cause, *1966*: July, 1079
Flagyl, *1967*: Sept., 1257
Fluids, body, cultures, in management of infections, *1966*: Sept., 1421
    electrolytes and, disturbances in cancer, *1966*: May, **711-732**
    excess of, in cancer, *1966*: May, 721
  gastrointestinal, loss of, disorders of renal function with, *1966*: July, 998
    retention of, disorders of renal function with, *1966*: July, 1000
  restriction, in refractory heart failure, *1968*: Sept., 1165
Fluids and electrolytes, depletion, in pyloric obstruction, therapy for, *1968*: Nov., 1333
Fluorescein angiography, of ocular fundus, *1968*: July, **853-869**
5-Fluorodeoxyuridine as anticancer agent, *1966*: May, 859, 864
9-α-Fluorohydrocortisone, for orthostatic hypotension, *1968*: July, 814
5-Fluorouracil, as anticancer agent, *1966*: May, 864
  for metastatic gastrointestinal cancer, *1966*: March, 428, 433
Flutter, atrial, propanolol for, *1968*: Sept., 1023
Folate, absorption, studies, *1968*: Nov., 1351
Folic acid, activity, effects of vitamin B_{12}, therapy on, *1966*: Nov., 1627, 1628, 1638
  antagonists, in gastrointestinal cancer, *1966*: March, 429

Folic acid (*Continued*)
  deficiency, anemia, *1966*: Nov., 1679
    laboratory diagnosis, *1966*: Nov., 1693, 1694
    mechanisms, *1966*: Sept., 1253
    vitamin B_{12} deficiency, clinical differentiation, *1966*: Sept., 1249
  therapy, for tropical sprue, *1968*: Nov., 1379
Follicle, graafian, steroid production by, *1967*: July, 906, 910
Food(s), allergy to, *1966*: March, 397
  poisoning, Salmonella, *1967*: May, 647
Foot, in rheumatoid arthritis, *1968*: May, 498
    surgery, *1968*: May, 729
Foreign travel, immunization for, *1967*: May, 843-846
Friedländer pneumonia, treatment, *1967*: March, 545
Friedreich's ataxia, *1968*: July, 900
Friedreich's sign in constrictive pericarditis, *1966*: Sept., 1233
Fundus of eye, fluorescein angiography, *1968*: July, **853-869**
Fungus infections, drugs in, and their indications, *1967*: Sept., **1181-1188**
    toxic reactions, *1967*: July, 926
  of lung, recognition and management, *1967*: March, **519-527**
Furocoumarins, photodermatitis due to, *1966*: Sept., 1301
Furosemide (Lasix), clinical use, *1967*: Sept., **1277-1283**
  for hypertension, *1968*: Sept., 1232
  for refractory heart failure, *1968*: Sept., 1172
Fusion beats, ectopic, *1966*: Jan., 54

GALACTOSEMIA, inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Gallops, atrial, *1966*: Sept., 1215
Gamma globulin in postoperative infections, *1966*: May, 800
Gammapathies, IgM, *1966*: May, 670
  IgG and IgA, *1966*: May, 669
Ganglion cells, dorsal root, degeneration, *1968*: July, 900
Gangrene, gas, hyperbaric oxygen in, *1967*: Sept., 1309
Gardner's syndrome, inheritance, *1968*: Nov., 1274
  and variants, *1966*: March, 382
Garymicin, *1967*: Sept., 1128
Gas gangrene, hyperbaric oxygen in, *1967*: Sept., 1309
Gas, inhaled, aerosol therapy, *1967*: March, 313
Gastrectomy, malnutrition caused by, *1968*: Nov., 1400
Gastric. See also *Stomach.*
Gastric analysis, *1968*: Nov., **1305-1313**
  in anemias, *1966*: Nov., 1695
  technique, *1968*: Nov., 1306
Gastric atony, vs. pyloric obstruction, *1968*: Nov., 1329
Gastric retention, vs. pyloric obstruction, *1968*: Nov., 1329
Gastric secretion, clinical aspects, *1968*: Nov., **1305-1313**
  tests, *1968*: Nov., 1307
Gastrin, effects, *1968*: Nov., 1270
  gastrointestinal disease and, *1968*: Nov., 1299
  implications of current research on, *1968*: Nov., 1269
  structure, secretion, and action, *1968*: Nov., 1298
Gastrocamera, *1966*: May, 755
Gastroenteritis, Salmonella, *1967*: May, 647
  viral, *1967*: May, 637
Gastroenterology, implications of current research in, *1968*: Nov., **1269-1272**
Gastrointestinal diseases, arthropathies with, *1966*: March, **417-425**
  autoimmune mechanisms and, *1968*: Nov., **1285-1295**
  clinical nutrition and, *1968*: Nov., **1397-1402**
  cutaneous melanosis with, *1966*: March, **347-602**
  cytological examination in, *1968*: Nov., **1315-1328**
  genetic aspects, *1968*: Nov., **1273-1283**
  renal consequences, *1966*: March, 511
  symposium on, *1968*: Nov., **1265-1501**
  with extragastrointestinal symptoms, genetic factors in, *1968*: Nov., 1276
Gastrointestinal effects of chemotherapy, *1966*: May, 751
Gastrointestinal fluid, loss, disorders of renal function with, *1966*: July, 998
Gastrointestinal function, altered, inheritance, *1968*: Nov., 1275
Gastrointestinal hemorrhage, disorders of renal function in, *1966*: July, 997
  in cancer, *1966*: May, 748
Gastrointestinal hormones, implications of current research in, *1968*: Nov., 1269
Gastrointestinal infection, articular manifestations, *1966*: March, 422
Gastrointestinal manifestations, of cancer, unusual, *1966*: May, **747-754**
  of connective tissue diseases, *1966*: March, 417
  of digitalis intoxication, *1966*: March, **501-506**

- Gastrointestinal manifestations *(Continued)*
  - of hypercalcemia, *1966*: March, **569-573**
  - of renal disease, *1966*: March, **507-514**
  - of thyroid disease, *1966*: March, **581-590**
- Gastrointestinal response to stress, *1966*: March, **591-595**
  - cancer of, articular manifestations, *1966*: March, 422
    - diagnosis, newer techniques, *1966*: May, **754-759**
    - metastatic, chemotherapy of, *1966*: March, **427-438**
  - hypersensitivity and, *1966*: March, **393-416**
  - systemic disease and, symposium on, *1966*: March, **347-602**
- Gastropathy, hypertrophic, lymphomas and, *1966*: May, 751
- Gastroscopy, emergency, in bleeding esophageal varices, *1968*: Nov., 1463
- Genetic factors, in gastrointestinal disease, *1968*: Nov., **1273-1283**
- Genetics, and cancer, *1966:* May, 875-885
  - principles, *1966*: March, 379
  - rheumatoid arthritis and, *1968*: May, 489-490
- Genitourinary tract, tuberculosis, *1966*: Sept., 1443
- Gentamicin, *1967*: Sept., 1128-1131, 1145
- Geriatrics, psychiatry in, *1967*: Nov., **1515-1527**
- German measles. See *Rubella.*
- Gigantism, *1968*: March, 376
- Gilbert's syndrome, *1968*: Nov., 1420
- Gingiva, hyperplasia, *1966*: March, 367
- Gingivitis, herpetic, *1966*: March, 364
- Globulin, gamma. See *Gamma globulin.*
- Glomerular filtration rate, regulation, *1968*: March, 269
- Glomerulitis, lupus, *1966*: July, 1120, 1122
- Glomerulonephritis, acute renal failure due to, *1967*: July, 996
  - lupus, *1966*: July, 1120, 1122
  - poststreptococcal, in children, *1966*: July, **1141-1158**
- Glomerulus, renal, *1966*: July, 930
- Glucagon test, in hypoglycemia, *1968*: March, 285
- Glucagonoma, *1968*: March, 298
- Glucose tolerance test, hypersomatotropism and, *1968*: March, 372
  - in hypoglycemia, *1968*: March, 285
- Gluten enteropathy, cutaneous melanosis with, *1966*: March, 350
  - systemic manifestations, *1966*: March, **515-527**
- Glutethimide, for pain, *1968*: Jan., 49
- Glyceryl guaicolate in chronic bronchitis, *1967*: Sept., 1177
- Goiter, causes, *1968*: March, 409
  - clinical aspects, *1968*: March, 411
  - exophthalmic, radioactive iodine therapy for, *1968*: March, 425
    - thyroid hormones in, *1966*: Sept., 1398
    - unusual manifestations, *1967*: July, **915-924**
  - laboratory tests in, *1968*: March, 412
  - nontoxic thyroid hormones in, *1966*: *Sept.*, 1397
  - single and multinodular, management, *1968*: March, **409-415**
  - therapy for, *1968*: March, 413
  - toxic. See *Hyperthyroidism.*
- Gold sodium thiomalate (Myochrysine), for rheumatoid arthritis, *1968*: May, 691, 735
- Gold therapy, for rheumatoid arthritis, *1968*: May, 691, **733-738**
  - juvenile, *1968*: May, 586
- Gold thioglucose (Solganol), for rheumatoid arthritis, *1968*: May, 691, 735
- Gonadotropin, assay of, in amenorrhea, *1968*: March, 349
  - secretion of, decreased, *1968*: March, 363
    - excess, *1968*: March, 359
- Gonads, disorders, in adrenocortical disease, *1967*: July, 885
  - hormones, influence on renal function. *1966*: July, 992
  - steroid synthesis by, *1967*: July, **903-913**
- Gonorrhea, epidemiology and prevention, *1967*: May, 735-751
- Gout, allopurinol in, *1967*: Sept., 1217
  - in myeloproliferative disorders, *1966*: May, 809
  - kidney disease and, *1966*: July, **1031-1042**
    - treatment, *1966*: July, 1038
  - synovianalysis in, *1966*: Sept., 1288, 1290
  - thrombosis and, *1967*: Jan., 158
  - varying picture in, *1967*: July, **1035-1040**
  - vs. rheumatoid arthritis, *1967*: July, 1036
- Graafian follicle, steroid production by, *1967*: July, 906, 910
- Grafts, vascular, synthetic, electron microscopic studies, *1967*: Jan., 148
- Gram-negative bacilli, infections due to, treatment, *1967*: Sept., **1127-1152**
- Granulocytopoiesis. See *Leukopoiesis.*
- Granuloma, rheumatoid, in rheumatoid arthritis, *1968*: May, 616

Granulomatoses, pulmonary, due to inhaled organic antigens, *1967*: March, **459-482**
Granulomatous colitis. See *Colitis, granulomatous.*
Graves' disease. See *Goiter exophthalmic.*
Griseofulvin in fungus infections, *1967*: Sept., 1186
  toxic reactions, *1967*: July, 927
Growth hormone. See *Somatotropin.*
  retardation, in gluten enteropathy, *1966*: March, 525
Guanethidine (Ismelin), for hypertension, *1967*: Jan., 33, July, 985; *1968*: Sept., 1233
Guillain-Barré syndrome, *1968*: Jan., 115
Guillain-Barré-Strohl syndrome, *1968*: July, 900
Guilt reactions in chronic illness, *1967*: Nov., 1405
Gynecography, in amenorrhea, *1968*: March, 351
Gynecologist, psychiatry for, *1967*: Nov., **1375-1380**
Gynecomastia in Graves' disease, *1967*: July, 917

HAMMAN-RICH syndrome, *1967*: March, 439
Hamycin in pulmonary mycoses, *1967*: March, 525
Hand, in rheumatoid arthritis, examination, *1968*: May, 495
    surgery, *1968*: May, 719
Hand-foot syndrome in sickle cell anemia, *1966*: Nov., 1526
Hand-shoulder-arm syndrome, *1968*: Jan., 155
Haptoglobin, plasma, in diagnosis of anemias, *1966*: Nov., 1698
Harvester's lung, *1967*: March, 460
Hashimoto's struma, chronic BFP test for syphilis in, *1966*: Sept., 1274, 1277
Head, and neck, carcinoma, gastrointestinal bleeding in, *1966*: May, 749
  local analgesia of, in office, *1968*: Jan., 180
Headache, chronic renal failure and, *1968*: July, 848
  exertional, benign, *1968*: July, **801-808**
  sudden, intracranial hemorrhage and, *1968*: Sept., 1198
Hearing, disturbed, cerebellopontine angle lesions and, *1968*: July, 789
    chronic renal failure and, *1968*: July, 847
Heart, anomalies, extrasystoles in, *1966*: Jan., 68
  arrest. See *Cardiac arrest.*
Heart (*Continued*)
  arrhythmias. See *Arrhythmias.*
  auscultation, *1966*: Sept., 1210
    functional tests as aid, *1966*: Jan., **73-89**
  beats, diastolic, *1966*: Sept., 1233
    ectopic, supraventricular, after myocardial infarction, *1968*: Sept., 1067
    premature, usefulness in cardiac diagnosis and prognosis, *1966*: Jan., **51-71**
      ventricular, propanolol for, *1968*: Sept., 1025
  block, after myocardial infarction, *1968*: Sept., 1069
    complete, pacemakers in, *1966*: Jan., 326
      phonocardiogram in, *1966*: Jan., 94
    permanent, causes of and surgery for, *1968*: Sept., 1126-1127
  carcinoid, malignant, *1966*: May, 739
  catheterization, ectopic beats in, *1966*: Jan., 68
    in constrictive pericarditis, *1966*: Sept., 1235
    in "stiff heart" syndrome, *1967*: July, 965
  disease, amyloid and other types, alcoholic myocardiopathy, *1968*: Sept., 1186
    atherosclerotic, myocardial infarction and, *1968*: Sept., 1061
    beriberi, *1966*: Jan., 303
    cholecystectomy in presence of, *1966*: March, **495-500**
    congenital, as a pathologic complex, *1966*: Jan., 3
      cyanotic, hyperbaric surgery for, *1967*: Sept., 1310
      fever in, *1966*: Jan., 215, 222
      in adult, *1966*: Jan., **15-35**
      pathology, newer concepts, *1966*: Jan., **3-14**
    conquest of, symposium on, *1966*: Jan., **1-341**
    coronary. See *Coronary artery disease.*
    diagnosis, auscultation in, functional tests as aid, *1966*: Jan., **73-89**
      phonocardiography in, *1966*: Jan., **91-109**
      radiologic techniques, *1966*: Jan., **127-139**
      serum enzymes in, *1966*: Jan., **171-191**
      usefulness of extrasystoles in, *1966*: Jan., **51-71**
    fever in, *1966*: Jan., **211-228**
    ischemic, fever in, *1966*: Jan., 215, 223

Heart (*Continued*)
- disease, kyphoscoliotic, *1966:* Jan., 46
  - pulmonary function in, *1966*: Jan., **141-157**
  - pulmonary hypertensive, diagnosis, *1966*: Jan., 38, 40
  - renal aspects, *1966*: Jan., **255-269**
  - rheumatic, angiocardiography in, *1966*: Jan., 130
    - fever in, *1966*: Jan., 215, 222
  - vs. malignancy of heart, *1966*: May, 743
- effects, of electrolyte abnormalities of cancer on, *1966*: May, 742
  - malignant tumors on, direct and indirect, *1966*: May, 739, 741
  - nonbacterial thrombotic endocarditis on, *1966*: May, 741
  - of pheochromocytoma on, *1966*: May, 740
- emphysema, *1966*: Jan., 45
- enlarged, with cyanosis and no murmurs, *1966*: Jan., 31
- examination, bedside, *1966*: Sept., **1203-1220**
- failure, after myocardial infarction, *1968*: Sept., 1071
  - congestive, dialysis for, *1968*: Sept., 1176
    - fever in, *1966*: Jan., 214
    - in chronic renal failure, *1966*: July, 1183
    - in coronary artery disease, *1967*: 942
    - liver disorders in, *1966*: March, **487-493**
      - treatment, *1966*: March, 491
    - nutrition in, *1966*: Jan., **301-307**
    - proteinuria in, *1966*: Jan., 260
    - renal pathophysiology, *1966*: Jan., 255
    - treatment, in respiratory failure, *1967*: March, 333
    - venous tone in, *1968*: Sept., 1081
    - vs. cancer of heart, *1966*: May, 743
  - due to alveolar hypoventilation, treatment, *1967*: March, 420
    - to "stiff heart" syndrome, *1967*: July, **959-966**
  - dysventilation syndrome with, diagnosis, *1966*: Jan., 39
  - following chronic pulmonary disease, classification, *1966*: Jan., 39
  - refractory, *1968*: Sept., **1157-1182**
    - factors in, *1968*: Sept., 1157-1162
  - serum enzymes in, *1966*: Jan., 183
- involvement, in cancer, *1966*: May, **733-746**
  - in rheumatoid arthritis, *1967*: July, 1022

Heart (*Continued*)
- involvement, in rheumatoid arthritis, juvenile, *1968*: May, 573
- murmurs, *1966*: Sept., 1210-1217
  - changes in intensity, following drug administration, *1966*: Jan., 78, 86
  - classification, *1966*: Jan., 103
  - in atrial septal defects, *1967*: July, 953
- pacemakers, clinical and physiologic studies, *1966*: Jan., **322-341**
- percussion, *1966*: Sept., 1208
  - jumping technique, *1966*: Sept., 1208, 1209
- rate, slowed, after myocardial infarction, *1968*: Sept., 1069
- resuscitation, serum lactic dehydrogenase in, *1966*: Jan., 200
- sounds, *1966*: Jan., 92-103, Sept., 1210-1217
  - classification, *1966*: Jan., 93
  - in atrial septal defects, *1967*: July, 953
  - second, in uncomplicated ventricular septal defect, *1966*: Jan., **111-114**
  - testing patients with, *1966*: Jan., **73-89, 91-109**
- "stiff," as cause of heart failure, *1967*: July, **959-966**
- surgery of, complications, fever in, *1966*: Jan., 217
  - serum enzymes in, *1966*: Jan., 187
- tumors, malignant, effect of therapy on, *1966*: May, 745
  - metastatic, *1966*: May, 734
  - vs. heart diseases, *1966*: May, 743
- valves, prosthetic, arrhythmias and, *1968*: Sept., 1138
  - failure, *1968*: Sept., 1135
  - hemolytic anemia and, *1968*: Sept., 1138
  - in acquired aortic stenosis, *1966*: Jan., 319
  - infection and, *1968*: Sept., 1136
  - management of patients with, *1968*: Sept., **1133-1143**
  - pregnancy and, *1968*: Sept., 1139

Helium-oxygen mixtures, in status asthmaticus, *1967*: March, 382

Hemangioma, intracranial, cerebellopontine angle syndrome and, *1968*: July, 793
- of choroid, fluorescein angiography of fundus in, *1968:* July, 858

Hematinics in anemia, *1966*: Nov., 1716

Hematocolpos in adolescence, *1965*: March, 490

Hematocrit, in rheumatoid arthritis, *1968*: May, 527

Hematologic, See also *Blood.*

Hematologic disorders, in aged persons, splenectomy for, *1966*: Nov., **1533-1558**
  symposium on, *1966*: Nov., **1485-1720**
Hematoma, intracerebral, treatment for, *1968*: Sept., 1208
Hematopoiesis, endocrine function and, *1968*: March, **231-241**
Hematuria, microscopic, in lupus nephritis, *1966*: July, 1121
Hemochromatosis, clinical description, *1966*: Nov., 1580
  hereditary aspects, *1966*: Nov., 1582; *1968*: Nov., 1276
  treatment, by phlebotomy, *1966*: Nov., **1579-1590**
Hemoglobin(s), A_2 and fetal determinations, *1966*: Nov., 1692
  binding capacity in diagnosis of anemias, *1966*: Nov., 1698
Hemoglobulinuria, renal failure in, *1967*: July, 997
Hemolytic anemia. See under *Anemia.*
Hemophilia, treatment, *1967*: Sept., **1241-1247**
Hemophilus influenzae pneumonia, treatment, *1967*: March, 545
Hemorrhage, antifibrinolytic therapy, *1967*: July, 1067
  effects on blood pressure, *1967*: July, 976
  esophageal varices and, diagnosis and treatment, *1968*: Nov., **1457-1474.** See also *Esophagus, varices, bleeding.*
  fibrinolytic, *1967*: July, **1061-1072**
  gastrointestinal, azotemia of, *1966*: March, 512
    disorders of renal function in, *1966*: July, 997
    in cancer, *1966*: May, 748
    in liver disease, *1967*: July, 1005
  prosthetic heart valves and, *1968*: Sept., 1135
  subarachnoid, acute, *1968*: Sept., 1194
  urinary, antifibrinolytic therapy, *1967*: July, 1068
  uterine, psychologic aspects, *1967*: Nov., 1376
    postpartum, antifibrinolytic therapy, *1967*: July, 1068
Hemorrhagic diathesis, anticoagulants in, *1966*: Nov., 1673
  combined therapy, *1966*: Nov., 1675
Hemorrhagic disorders, aminocaproic acid in, complications, *1966*: Nov., 1669
  in liver disease, *1966*: March, 544
Hemostasis, abnormal, in liver disease, *1966*: March, 544, 548
  biochemical aspects, *1966*: Sept., **1257-1270**
Henle's loop, *1966*: July, 933
Heparin, effects, *1967*: Jan., 151
  for "impending coronary syndrome," *1968*: Sept., 1062
  in status asthmaticus, *1967*: March, 380
Hepatic coma, ammonia toxicity and, *1968*: Nov., 1477
  management, *1968*: Nov., **1479-1481**
  trials of treatment, *1968*: Nov., 1479
Hepatitis, cholangiolitic, *1968*: Nov., 1421
  infectious, changing trends, *1967*: May, **653-660**
    vs. serum hepatitis, *1967*: May, 658
  in liver disease, *1967*: July, 1003
  lupoid, autoimmunity and, *1968*: Nov., 1290
  serum, vs. infectious hepatitis, *1967*: May, 658
  viral, *1967*: May, **653-660**
Hepatolenticular degeneration, *1968*: July, 989
  inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Hepatology, implications of current research in, *1968*: Nov., **1403-1406**
Heredity, as coronary risk factor, *1966*: Jan., 243
  in cancer, *1966*: May, **875-885**
  principles, *1966*: March, 379
Herniated disk, cervical root pain and, *1968*: July, 775
Herpangina in children, *1967*: May, 822
Herpes virus infections in children, *1967*: May, 822
Herpes zoster, pain in, *1968*: Jan., 115
Hetacillin, *1967*: Sept., 1115
Hexamethonium in hypertension, *1967*: July, 989
Hicks, foot ulcer of, *1968*: July, 899
Hip, in rheumatoid arthritis, *1968*: May, 501
    surgery, *1968*: May, 725
Hirsutism, drugs and other agents inducing, *1967*: July, 897
  in adrenocortical disease, *1967*: July, 886
  in women, classification, *1967*: July, 894
Histamine, rheumatoid arthritis inflammation and, *1968*: May, 625
Histamine antagonists. See *Antihistamines.*
Histamine test, for pheochromocytoma, *1968*: Sept., 1220
  of gastric secretion, *1968*: Nov., 1307-1310
Histoplasmosis, of adrenal glands, *1968*: March, 329
  pulmonary, *1967*: March, **519-527**

- History, medical, in hypertensive disease, *1967*: Jan., 16
  - taking, for comprehensive diagnosis, *1967*: Nov., 1383
    - in psychosomatic disease, *1967*: Nov., 1415
- HMG-Ortho, *1967*: Sept., 1267
- Hodgkin's disease, chromosomal alterations in, *1966*: May, 881
  - jaundice in, *1966*: May, 754
  - lymphangiography in, *1966*: May, **675-688**; *1967*: Jan., 237, 241
  - pathogenesis, classification and treatment, *1966*: May, **819-832**, *Nov.*, **1591-1610**
  - with splenomegaly in elderly, splenectomy for, *1966*: Nov., 1538
- Home, adolescent problems in, *1967*: Nov., 1440
- Homosexual in syphilis control, *1967*: May, 747
- Honeycomb lung in diffuse interstitial pulmonary fibrosis, *1967*: March, 441
- Hormones, adenohypophyseal, secretion of, decreased, *1968*: March, 362
      - excess, *1968*: March, 359
  - antidiuretic, and hypertension, *1967*: Jan., 9
    - influence on renal function, *1966*: July, 986
    - production, by nonendocrine cancer, *1966*: May, 764
    - secretion, deficient, polyuria and, *1968*: March, 384
      - disorders, *1968*: March, **381-391**
      - inappropriate, *1968*: March, 388-390, July, **817-826**
  - assays, in adrenocortical disease, *1967*: July, 890, 898
  - cytology, in cancer diagnosis, *1966*: May, 653
  - gastrointestinal, *1968*: Nov., **1297-1303**
    - implications of current research in, *1968*: Nov., 1269
  - growth. See *Somatotropin.*
  - influence on renal function, *1966*: July, **985-995**
  - pituitary. See *Hormones, adenohypophyseal.*
  - sex, erythropoiesis and, *1968*: March, 232
  - steroid, as anticancer agents, *1966*: May, 859, 864
  - therapy with. See *Endocrine therapy.*
  - thyroid, diagnostic uses, *1966*: Sept., 1399
    - preparations, *1968*: March, 434, 439
    - therapeutic use, *1966*: Sept., **1393-1402**
    - secretion, normal, *1968*: March, 431
      - variations in, *1968*: March, 437
- Hormone-producing cancers of nonendocrine origin, *1966*: May, 763-778
- Horner's pupil, *1968*: July, 879
- Hospital, state, role in practice of medicine, *1967*: Nov., **1467-1475**
- HPL. See *Lactogen, human placental.*
- Hydantoins, for seizures, *1968*: July, 963
- Hydralazine (Apresoline), for hypertension, *1966*: Jan., 298; *1967*: Jan., 31, July, 989; *1968*: Sept., 1233
  - for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1150
  - neurologic side effects, *1968*: July, 850
- Hydrarthrosis, intermittent, vs. rheumatoid arthritis, *1968*: May, 510
- Hydrocortisone, for rheumatoid arthritis, *1967*: Sept., 1214; *1968*: May, 743
- Hydronephrosis, intrarenal arteriogram in, *1967*: Jan., 61, 62
- Hydroxychloroquine, for rheumatoid arthritis, *1968*: May, 761
- Hydroxyproline, urinary, hyperparathyroidism and, *1968*: March, 458
- Hydroxystilbaminide, for fungus infections, *1967*: Sept., 1188
- 5-Hydroxytryptamine, rheumatoid arthritis inflammation and, *1968*: May, 625
  - for pulmonary blastomycosis, *1967*: March, 525
- Hydroxyurea as anticancer drug, *1966*: May, 867
- Hyperabduction syndrome, *1968*: July, 777
- Hyperaldosteronism, diagnosis, *1967*: Jan., 21
  - hypertension and, *1967*: July, 973
  - primary, etiology and diagnosis, *1967*: July, **883-901**
  - secondary to congestive heart failure, *1966*: Jan., 257
- Hyperbaric oxygen, rationale, physiology, and clinical uses, *1967*: Sept., **1301-1314**
- Hypercalcemia, gastrointestinal manifestations, *1966*: March, **569-573**
  - in cancer, *1966*: May, 729, 772
    - effects on heart, *1966*: May, 743
    - of breast, *1967*: July, 1090
    - of lung, treatment, *1967*: March, 571
  - in hypernephroma, *1966*: July, 1081
  - in hyperparathyroidism, *1967*: July, 871, 880
  - in hyperthyroidism, *1967*: July, 923
- Hypercholesterolemia, as coronary risk factor, *1966*: Jan., 231
  - therapy for, diet, *1968*: Sept., 1251-1253
      - drug, *1968*: Sept., 1253-1259
- Hypercortisonism, with rheumatoid arthritis, *1968*: May, 740-742

Hypercreatinemia, myopathy and, *1968*: March, 247
Hyperdynamic states of cardiovascular system, adrenergic receptor blockers and, *1968*: Sept., **1041-1048**
Hyperkalemia, cardiovascular effects of, *1968*: Sept., 1241
  causes of, *1968*: Sept., 1243
  in cancer, *1966*: May, 725
  in renal failure, *1966*: July, 1180
Hyperkinetic heart syndrome, adrenergic receptor blockers and, *1968*: Sept., 1044
Hyperlipemia, acute pancreatitis and, *1966*: March, 450; *1968*: Nov., **1493-1501**
Hypermenorrhea, oral contraceptive drugs and, *1967*: Sept., 1271, 1272
Hypernatremia in cancer, *1966*: May, 719
Hypernephroma, *1966*: July, **1067-1083**
  arteriogram in, *1967*: Jan., 52, 53, 61, 63
Hyperparathyroidism, clinical manifestations, *1967*: July, 876
  familial, *1967*: July, 875
  pancreatitis with, *1966*: March, 450, Sept., **1403-1418**
  peptic ulcer with, *1966*: March, 571, Sept., **1403-1418**
  presymptomatic, *1967*: July, 875
  primary, *1967*: July, **871-881**
    diagnosis, *1968*: March, **451-462**
Hyperphosphatemia in renal failure, *1966*: July, 1180
Hyperpigmentation. See under *Pigmentation.*
Hypersensitivity, drug, cutaneous manifestations, unusual, *1967*: July, **1073-1088**
  gastrointestinal tract and, *1966*: March, **393-416**
  reactions, *1966*: March, 394
Hypersomatotropism, diagnosis, *1968*: March, **371-380**
Hypersplenism, in elderly, splenectomy for, *1966*: Nov., **1533-1558**
  in rheumatoid arthritis, *1968*: May, 529
Hypertension, aldosteronism and, differentiation, *1967*: July, 864
  as coronary risk factor, *1966*: Jan., 236
  biochemical factors, *1967*: July, 977
  diagnosis, *1967*: Jan., **15-24**
  drugs for, *1967*: Jan., 29, July, 985
    mild, *1967*: Jan., 30
  essential, *1966*: Jan., 295; *1967*: July, **977-993**
  etiologic aspects, *1967*: July, 969
  fluorescein angiography of fundus in, *1968*: July, 859
  hemorrhagic stroke and, *1968*: Sept., 1204-1206

Hypertension (*Continued*)
  in adrenocortical disease, *1967*: July, 886
  in chronic renal failure, *1966*: July, 1183
  in coarctation of aorta, *1967*: July, 971
  in hyperaldosteronism, *1967*: July, 973
  in parenchymal renal disease, *1966*: July, 1010
  in pheochromocytoma, *1967*: July, 971
  in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1143, 1150
  in toxemia of pregnancy, *1967*: July, 971
  mortality ratio, relationships with age and life expectancy, *1966*: Jan., 288-290
  natural history, *1967*: July, 968
  office management, *1966*: Jan., **287-299**
  pathophysiology, *1967*: Jan., **3-10**, July, 973
  portal, assessment, *1968*: Nov., 1414
  primary, renal function in, *1966*: July, 1008
    therapy for, *1968*: Sept., 1230-1233
  pulmonary heart disease with, *1966*: Jan., 38, 40
    in differentiation of bronchitis and emphysema, *1967*: March, 289
    with cardiac shunts, *1966*: Jan., 42
    with intrapulmonary shunts, *1966*: Jan., 43
  renal, *1966*: Jan., 294
    mechanisms producing, *1967*: Jan., 5
    surgery for, kidney function after, *1967*: Jan., **39-46**
    treatment, *1968*: Sept., 1230
  renal artery stenosis in, *1967*: Jan., 52, 54
  renal function in, *1966*: July, **1007-1020**
  renovascular, kidney function in, *1966*: July, 1014
    surgical treatment, *1967*: Jan., 217, 223
  risk of stroke in, *1967*: Jan., 109
  secondary, causes, *1968*: Sept:, 1214
    diagnosis, *1967*: Jan., 18, July, 971
      progress in, *1968*: Sept., **1213-1226**
    treatment, *1968*: Sept., 1227-1230
    vs. primary (essential), *1968*: Sept., 1213
  surgically remediable, *1966*: Jan., 293
  toxemia of pregnancy and, *1968*: Sept., 1234
  treatment, and its complications, *1967*: Jan., 28, July, 985, 987
    emergency, *1967*: Jan., 35
    physiologic and pharmacologic basis for, *1967*: Jan., **25-37**

- Hypertension (*Continued*)
  - treatment, recent advances in, *1968*: Sept., **1227-1236**
  - vs. alcoholic myocardiopathy, *1968*: Sept., 1186
  - with renal insufficiency, *1968*: Sept., 1234
- Hyperthyroidism, Addison's disease and, *1968*: March, 335, 336
  - apathetic or depleted, *1966*: March, 575; *1967*: July, 921
  - cardiovascular effects of, adrenergic receptor blockers and, *1968*: Sept., 1046
  - clubbing of fingers and toes in, *1968*: March, **393-398**
  - erythropoiesis and, *1968*: March, 235
  - exophthalmos with, surgery for, *1968*: March, **399-407**
  - gastrointestinal manifestations, *1966*: March, **581-590**
  - in nonthyroid cancer, *1966*: May, 775
  - leukopoiesis and, *1968*: March, 239
  - periosteal bone formation in, *1968*: March, **393-398**
  - unusual manifestations, *1967*: July, **915-924**
  - vs. euthyroidism, thyroid hormones in differentiation, *1966*: Sept., 1400
- Hyperuricemia, causes, *1966*: July, 1031
  - in cancer, *1966*: May, 728
  - in myeloproliferative disorders, *1966*: May, 809
  - in polycythemia vera, management, *1966*: Nov., 1512
  - renal damage from, *1966*: July, 1034
  - treatment, *1966*: July, 1036
- Hyperventilation, alveolar, *1967*: March, 409
  - in diffuse interstitial pulmonary fibrosis, *1967*: March, 444
- Hypnosis, for pain, *1968*: Jan., **217-224**
  - essential elements, *1968*: Jan., 218
  - hazards, *1968*: Jan., 222
  - in labor, *1968*: Jan., 145
- Hypnotics, nonbarbiturate, for pain, *1968*: Jan., 49
- Hypoadrenalism, idiopathic, parietal cell antibody and, *1968*: Nov., 1286
- Hypocalcemia, in cancer, *1966*: May, 729
  - in gluten enteropathy, *1966:* March, 521
  - in renal failure, *1966*: July, 1180, 1181
- Hypochondriasis in chronic illness, *1967*: Nov., 1405
- Hypogammaglobulinemia, arthritis of, vs. juvenile rheumatoid arthritis of polyarticular onset, *1968*: May, 578
- Hypoglycemia, causes, *1968*: March, 283
  - in nonpancreatic cancer, *1966*: May, 766
- Hypoglycemia (*Continued*)
  - insulinoma and, tolbutamide and leucine tests in, *1968:* March, **283-294**
  - pregnancy and, *1968*: March, 256
  - spontaneous, in pancreatic disease, *1966*: March, 455
- Hypokalemia, cardiovascular effects of, *1968*: Sept., 1241
  - clinical manifestations of, *1968*: Sept., 1104
  - diseases causing, *1967*: July, 894
  - disorders of renal function with, *1966*: July, 1002
  - heart failure due to, *1966*: Jan., 305
  - hypertension and, *1968*: Sept., 1216
  - in cancer, *1966*: May, 724
    - effects on heart, *1966*: May, 742
  - in gluten enteropathy, *1966*: March, 526
  - in renal failure, *1966*: July, 1180
- Hyponatremia, in cancer, *1966*: May, 721, 764
  - recognition, *1968*: July, 817
- Hypoparathyroidism, skeletal metabolism in, kinetic studies, *1965*: Jan., 251
- Hypophysectomy for carcinoma of breast, *1966*: Sept., 1463
- Hypophysis. See *Pituitary gland.*
- Hypopituitarism, amenorrhea and, *1968*: March, 342
- Hypoplasia of aorta, pathologic complexes, *1966*: Jan., 11
- Hypoproteinemia in gluten enteropathy, *1966*: March, 522
- Hypoprothrombinemia in gluten enteropathy, *1966*: March, 524
- Hypotension, after myocardial infarction, *1968*: Sept., 1072
  - orthostatic, *1968*: July, **809-816**
  - venous tone in, *1968*: Sept., 1082
- Hypothalamic discharge, periodic, *1966*: March, 371
- Hypothalamus, amenorrhea and, *1968*: March, 340
  - in production of hypertension, *1967*: Jan., 9
  - in regulation of adenohypophyseal hormone secretion, *1968*: March, 358
- Hypothermia, esophagogastric, for bleeding esophageal varices, *1968*: Nov., 1466
- Hypothyroidism. See also *Myxedema.*
  - Addison's disease and, *1968*: March, 334, 336
  - after radioactive iodine therapy, *1968*: March, **417-429**
  - autoimmunity in, *1965*: Nov., 1688
  - cardiovascular disease and, *1968*: March, 440
  - erythropoiesis and, *1968*: March, 235
  - gastrointestinal manifestations, *1966*: March, 586

Hypothyroidism (*Continued*)
  thyroid hormones in, *1966*: Sept., 1395
  treatment, evaluation of, *1968*: March, 441
    primary, *1968*: March, 431
Hypouricemia in cancer, *1966*: May, 728
Hypoventilation, alveolar, *1967*: March, 412
  mechanical, heart failure in, *1966*: Jan., 46
  of obesity, heart failure in, *1966*: Jan., 47
Hypoxemia, arterial, in differentiation of bronchitis and emphysema, *1967*: March, 288
  in acute respiratory failure management, *1967*: March, 328
Hypoxia, cardiovascular response to, adrenergic receptor blockers and, *1968*: Sept., 1044
Hysterical patient, psychologic evaluation in, *1967*: Nov., 1480

ICTERUS. See *Jaundice.*
Icterus intermittens juvenalis, *1968*: Nov., 1420
"Ileitis, backwash," *1968*: Nov., 1387
"Ileocolitis," *1968*: Nov., 1387
Ileus, metabolic, in uremia, *1966*: March, 510
Iminodibenzyl antidepressants, tricyclic, *1967*: Nov., 1460, 1461
Imipramine in alcoholism, *1967*: Sept., 1253
Immunity, alterations in, rheumatoid arthritis and, *1968*: May, 594-598
  rheumatoid arthritis inflammation and, *1968*: May, 630-631
Immunization, active, of children, *1967*: May, **581-586**
  ARD, *1967*: May, 773, 776
  cholera, *1967*: May, 630
  common cold, *1967*: May, 767
  for foreign travel, *1967*: May, **843-846**
  infectious diseases, symposium on, *1967*: May, **579-846**
  influenza, *1967*: May, **781-790**
    in infants and children, *1967*: May, 584
  measles, *1967*: May, 583, **599-608**
  pneumonia, atypical, progress in developing, *1967*: May, 798
  poliomyelitis, *1967*: May, **681-692**
  programs, community organization for, *1967*: May, **837-842**
    national, current status, *1967*: May, 831-835
  rabies, *1967*: May, **693-700**
    encephalitis following, *1967*: May, 707
Immunization (*Continued*)
  respiratory disease, acute, *1967*: May, 816
  rubella and rubella syndrome, *1967* May, **587-598**
  smallpox, encephalitis following, *1967*: May, 704
    in infants and children, *1967*: May, 584
  tuberculosis, *1967*: May, **753-764**
    in infants and children, *1967*: May, 582
  typhoid fever, *1967*: May, **617-623**
  virus diseases, vector-borne, *1967*: May, **673-679**
  yellow fever, *1967*: May, 673
Immunoglobulins, definition and nature, *1966*: Nov., 1487
  metabolism, *1966*: Nov., **1487-1499**
  monoclonal, in cancer, *1966*: May, 667-674
Immunologic factors in farmer's lung, *1967*: March, 470
Immunology, of tumors, *1966*: May, **901-912**
Immunoprophylaxis of arthropod-borne virus diseases, *1967*: May, **673-679**
Immunosuppressive drugs, for rheumatoid arthritis, *1967*: Sept., 1220
  for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1150
  for renal transplantation, *1966*: July, 1166
  for status asthmaticus, *1967*: March, 380
Impending coronary syndrome, *1968*: Sept., 1062
Inderal, *1967*: Sept., 1225
Inderan. See *Propanolol.*
Indomethacin, for rheumatoid arthritis, *1967*: Sept., 1217; *1968*: May, 694
Infantile spasms, medical treatment for, *1968*: July, 967
Infants, diarrhea, *1967*: May, 643
  immunization, routine, *1967*: May, 581
Infarction, myocardial. See under *Myocardium.*
  renal, hypertension in, *1966*: July, 1012
Infection(s), anemias, *1966*: Nov., **1703-1712**
  as cause of rheumatoid arthritis, *1968*: May, **673-676**
  bacterial, management of, role of microbiological laboratory in, *1966*: Sept., **1419-1432**
  encephalitis following, *1967*: May, **701-717**
  gram-negative bacilli, new antibiotics in, *1967*: Sept., **1127-1152**
  in cancer patients undergoing surgery, treatment, *1966*: May, **791-802**

Infection(s) *(Continued)*
  mycobacterial, atypical, pathogenesis, clinical manifestations, and treatment, *1967*: March, **503-517**
  mycotic, systemic, recognition and management, *1967*: March, **519-527**
  treatment, in acute respiratory failure, *1967*: March, 331
    in status asthmaticus, *1967*: March, 387
  urinary tract, etiology, diagnosis and treatment, *1966*: July, **1127-1135**
  viral. See *Viral infections.*
Infectious diseases, prevention and immunization, symposium on, *1967*: May, **579-846**
Inflammation, vascular, electron microscopic studies, *1967*: Jan., 146
Influenza, epidemic, immunization and control, *1967*: May, **781-790**
  immunization, *1967*: May, 783
  vaccines, *1967*: May, 783
    in infants and children, *1967*: May, 584
    purified antigens, *1967*: May, 786
    with mineral oil adjuvants, *1967*: May, 785
  virus infections, in adults, *1967*: May, 811, 812
    in children, *1967*: May, 827
Inhalation therapy, *1967*: March, **307-321**
Inheritance. See *Heredity.*
Injuries. See names of parts or organs.
Inspection in heart examination, *1966*: Sept., 1204
Insulin, in diabetes, *1966*: Sept., 1379
  influence on renal function, *1966*: July, 993
  plasma, assay of, in hypoglycemia, *1968*: March, 285
  production in nonpancreatic cancer, *1966*: May, 766
  secretion, *1968*: March, 284
Insulin antagonism, pregnancy and, *1968*: March, 254
Insulin test, of gastric secretion, *1968*: Nov., 1309
Insulin tolerance test, hypersomatotropism and, *1968*: March, 372
  in hypoglycemia, *1968*: March, 285
Insulinoma, *1968*: March, 300
  tolbutamide and leucine tests in, *1968*: March, **283-294**
Intercostal block, in office, *1968*: Jan., 180
Internal medicine, role of psychiatry in, *1967*: Nov., 1410
  scope of, past and present, *1967*: Nov., 1411
Internist, psychiatry and, *1967*: Nov., **1409-1423**
Interstitium, renal, *1966*: July, 934
Interventricular septum, rupture of, after myocardial infarction, *1968*: Sept., 1074
Intervertebral disk, herniated, cervical root pain and, *1968*: July, 775
Interview, continuance, through physical examination, *1967*: Nov., 1392
  focus and channeling, *1967:* Nov., 1388
  in psychosomatic disease, *1967*: Nov., 1415
  initial, in comprehensive diagnosis, *1967*: Nov., 1387
Intestines, diseases, disorders of renal function in, *1966*: July, **997-1006**
    nonspecific inflammatory, *1968*: Nov., **1387-1396**
  infections, current problems, *1967*: May, **609-615**
    incidence and control, influence of age and nutrition on, *1967*: May, **643-652**
  lipodystrophy, cutaneous melanosis with, *1966*: March, 351
  malabsorption in. See under *Malabsorption.*
  polyps of, inheritance, *1966*: March, **379-392**; *1968*: Nov., 1274
Intrarenal arteries, lesions, arteriography in, *1967*: Jan., 60
Involutional melancholia, internist's role, *1967*: Nov., 1421
Iodides, organic, in investigation of coexisting gastrointestinal and thyroid disease, *1966*: March, 588
Iodine, deficiency of, goiter and, *1968*: March, 409
  protein-bound, thyroid function and, *1968*: March, 464
    thyroid therapy and, *1968*: March, 442
  radioactive, biologic effects, *1968*: March, 419
    dosage, *1968*: March, 417
    in treatment of thyrotoxicosis, *1968*: March, **417-429**
    post-therapy management, *1968*: March, 423
    principles of therapy, *1968*: March, 422-427
    uptake test, *1968*: March, 464
Iododermas, circumscribed, *1967*: July, 1083
Ion solutions, balanced, in hypovolemic shock, *1967*: Jan., 91
IPPB. See *Breathing, intermittent positive pressure.*
Iron, absorption, normal, *1968*: Nov., 1343
    studies, *1968*: Nov., 1351
  body, *1966*: Nov., 1579
  deficiency, anemia of. See under *Anemia.*

Iron (*Continued*)
  deficiency, hypothyroidism and, *1968*: March, 237
  in polycythemia vera, *1966*: Nov., 1514
  metabolism of, in rheumatoid arthritis, *1968*: May, 529
  parenteral, in anemia, *1966*: Nov., 1717
  slow-release tablets, in anemia, *1966*: Nov., 1716
  storage disease, clinical description, *1966*: Nov., 1580
    treatment by phlebotomy, *1966*: Nov., **1579-1590**
  studies, in anemia, *1966*: Nov., 1692
Irradiation. See *Radiation, Radium, Roentgen.*
Irritable colon, *1966*: March, **591-595**
Ischemia, cardiac, transient, myocardial infarction and, *1968*: Sept., 1062
  cerebral, hyperbaric oxygen in, *1967*: Sept., 1311
  limb, acute, low molecular weight dextran for, *1967*: Sept., 1293
    hyperbaric oxygen in, *1967*: Sept., 1312
Islet cells, of pancreas. See under *Pancreas.*
Ismelin. See *Guanethidine.*
Isoimmunization, following platelet transfusions, *1966*: Nov., 1565
  incompatibility problems, *1966*: Nov., 1648
Isoniazid, in tuberculosis, *1966*: Sept., 1435, 1436
  of kidney, *1966*: July, 1138
Isoproterenol (Isuprel), as aerosol, *1967*: March, 310
  as aid to cardiac auscultation, *1966*: Jan., 84, 87
  for shock, *1968*: Sept., 1085
    hypovolemic, *1967*: Jan., 94
    of myocardial infarction, *1967*: Jan., 71, 73, 77
  for slow ventricular rate, *1968*: Sept., 1070
  for status asthmaticus, *1967*: March, 380
  vascular effects, *1967*: July, 992
Isotopes, radioactive, in chronic granulocytic anemia, *1966*: May, 805
    in evaluation of renal function, *1966*: July, **937-955**
    in Hodgkin's disease, *1966*: May, 828
    scanning, in bone metastases, *1966*: May, **701-710**
      in cancer diagnosis, *1966*: May, **689-700**
Isuprel. See *Isoproterenol.*
Itching. See *Pruritus.*

JAFFE'S tests, in Horner's pupil, *1968*: July, 879, 880
Jaundice, age of patient and cause, *1968*: Nov., 1424
  cholestatic, of pregnancy, *1968*: Nov., 1422
  classification, *1968*: Nov., 1420
  differential diagnosis, *1968*: Nov., **1417-1444**
  drug-induced, *1968*: Nov., 1422
  hepatic, *1968*: Nov., 1420, 1421
  hepatocanalicular, *1968*: Nov., 1420, 1421
  hepatocellular, *1968*: Nov., 1420, 1421
  in Hodgkin's disease, *1966*: May, 754
  mode of onset and cause, *1968*: Nov., 1425
  nonhemolytic, hereditary, *1968*: Nov., 1420
  pain and, *1968*: Nov., 1426
  physical examination and, *1968*: Nov., 1426
  posthepatic, *1968*: Nov., 1420, 1423
  prehepatic, *1968*: Nov., 1420
  production, *1968*: Nov., 1420, 1421
  retention, *1968*: Nov., 1420
Joint space, narrowing of, in rheumatoid arthritis, *1968*: May, 660
Joints, in rheumatoid arthritis, ankylosis, *1968*: May, 614
    aspiration, *1968*: May, 539
    effusion, *1968*: May, 609
    examination, *1968*: May, 494
    inflammatory changes, *1968*: May, 611
    lymphoid nodules, *1968*: May, 610
    malalignment, *1968*: May, 660
    ankylosing spondylitis, *1968*: May, 518
  of spine, osteoarthritis of, low back pain and, *1968*: Jan., 62
  pathologic changes in, rheumatoid arthritis and, *1968*: May, 607-616
  peripheral, in ankylosing spondylitis, *1968*: May, 522
  soft tissue changes in, rheumatoid arthritis and, *1968*: May, 656
  subluxation of, in rheumatoid arthritis, *1968*: May, 660
  symptoms, in hyperparathyroidism, *1967*: July, 878
  tuberculosis, *1966*: Sept., 1443
JRA. See *Arthritis, rheumatoid, juvenile.*

KALLIKREIN, formation of bradykinin and, *1968*: March, 266

- Kallikrein-kininogen-kinin system, rheumatoid arthritis inflammation and, *1968*: May, 624
- Kanamycin, for drug-resistant tuberculosis in children, *1967*: Sept., 1156, 1162, 1163
  - for tuberculosis, *1966*: Sept., 1437, 1439
  - toxic reactions, *1967*: July, 933
- Keflin, *1967*: Sept., 1128
- Keflordin, *1967*: Sept., 1128
- Keratosis blenorrhagica, with arthritis, *1968*: May, 504
- Kidney. See also *Renal.*
  - abdominal aortic aneurysm and, *1966*: July, **1021-1030**
  - abscess, arteriogram in, *1967*: Jan., 61, 64, 65
  - arteriography, *1967*: Jan., **47-67**
  - artificial, early development, *1966*: Sept., 1352
    - some approaches to improved design and function, *1966*: Sept., **1351-1369**
  - biopsy, in toxemia of pregnancy, *1966*: July, 1051
    - in urinary tract infection, *1966*: July, 1132
  - circulation in, angiotensin and, *1968*: March, 269-275
  - cystic, congenital, pathogenesis, diagnosis and treatment, *1966*: July, **1101-1117**
    - radiograms in, *1967*: Jan., 61, 63, 66
  - disease(s), analgesic, *1966*: July, **1085-1090**
    - cardiovascular aspects of, *1968*: Sept., **1237-1247**
    - diagnosis, drip-infusion urography and nephrotomography in, *1966*: July, **957-967**
    - gastrointestinal disease and, interrelationships, *1966*: March, **507-514**
    - gouty, *1966*: July, **1031-1042**
      - treatment, *1966*: July, 1038
    - hypertensive, *1966*: July, 294; *1967*: Jan., 21
    - in gluten enteropathy, *1966*: March, 526
    - parenchymal, with hypertension, *1966*: July, 1010
    - polycystic, congenital, *1966*: July, **1101-1117**
      - hypertension and, *1968*: Sept., 1217
    - polyuria in, *1968*: March, 384
    - pulmonary involvement in, *1966*: July, **1055-1066**
    - secondary hypertension and, *1968*: Sept., 1214
    - symposium on, *1966*: July, **925-1186**
- Kidney (*Continued*)
  - disease(s), unilateral, diagnosis of, *1968*: Sept., 1221
    - uric acid, *1966*: July, **1031-1042**
      - in myeloproliferative disorders, *1966*: May, 809
      - treatment, *1966*: July, 1038
  - failure, acute, unusual causes and manifestations, *1967*: July, **995-1002**
    - chronic, conservative management, *1966*: July, **1175-1186**
      - metabolic abnormalities in, *1966*: July, 1176
      - neurologic complications of, *1968*: July, **845-851**
    - following surgical treatment of abdominal aortic aneurysm, *1966*: July, 1027
    - oliguric, use of mannitol in, *1966*: July, **1159-1163**
  - fistula, arteriovenous, arteriogram in, *1967*: Jan., 64
  - function, after surgery for renal hypertension, *1967*: Jan., **39-46**
    - disorders of, with intestinal diseases, *1966*: July, **997-1006**
    - during and after surgery, *1966*: July, **979-983**
    - effect of diagnostic and therapeutic roentgenologic procedures on, *1966*: July, **969-977**
    - evaluation by isotope techniques, *1966*: July, **937-955**
    - hormonal influence on, *1966*: July, **985-995**
    - in abdominal aortic aneurysm, assessment of, *1966*: July, 1029
    - in primary, renal and renovascular hypertension, *1966*: July, **1007-1020**
    - in toxemia of pregnancy, *1966*: July, 1047
  - hypoplastic, congenital, arteriogram in, *1967*: Jan., 51
  - in toxemia of pregnancy, *1966*: July, **1043-1053**
  - infarction, hypertension in, *1966*: July, 1012
  - insufficiency, hypertension and, *1968*: Sept., 1234
  - involvement, in hyperparathyroidism, *1967*: July, 878
  - ischemia of, renin-angiotensin system and, *1968*: March, 270
  - lesions, in heart disease, *1966*: Jan., **255-269**
    - in ulcerative colitis, *1966*: March, 532
  - necrosis, papillary, due to phenacetin, *1966*: July, 1085
  - photoscanning, *1966*: July, 947-954

- Kidney (*Continued*)
  - roentgen study, with isotopes, *1966*: July, 941-947
  - stones, drugs causing, *1966*: March, 570
    - urate, *1966*: July, 1035
  - structure, *1966*: July, **927-935**
  - transplantation, pneumonia following, *1966*: July, 1057
    - present status, *1966*: July, **1165-1173**
  - tuberculosis, arteriogram in, *1967*: Jan., 65
    - diagnosis and treatment, *1966*: July, **1137-1139**
  - tumors, hypertension and, *1966*: July, 1014; *1968*: Sept., 1217
  - vascular disease, hypertensive, *1966*: July, 1014
    - in pregnancy, *1966*: July, 1050
- Klebsiella infections, cephalothin in, *1967*: Sept., 1142
- Klebsiella pneumonia, treatment, *1967*: March, 545
- Knee, in rheumatoid arthritis, *1968*: May, 499
  - surgery, *1968*: May, 726
  - synovitis, *1967*: July, 1024
- Kwashiorkor, *1968*: Nov., 1361
- Kyphoscoliosis, alveolar hypoventilation in, *1967*: March, 415
- Kyphoscoliotic heart disease, *1966*: Jan., 46

- Labor, pain relief in, *1968*: Jan., **137-146**
- Lactase, deficiency, *1968*: Nov., 1358
- Lactic dehydrogenase, serum, in diagnosis of myocardial and other organ injury, *1966*: Jan., **193-209**
  - test for, *1968*: Nov., 1410, 1431
- Lactogen, human placental, insulin antagonism and, *1968*: March, 254
- Lanatoside C, for shock of myocardial infarction, *1967*: Jan., 71, 73, 77
- Landry's paralysis, *1968*: July, 901
- Laparotomy, negative, in hypernephroma, *1966*: July, 1076
- Largon. See *Propriomazine.*
- Laryngotracheobronchitis in children, *1967*: May, 823
- Larynx, topical analgesia, *1968*: Jan., 178
- Lasix. See *Furosemide. 1967*: Sept., 1277
- Lateral sclerosis, amyotrophic, speech disturbances in, *1968*: July, 838-842
- Leg, local analgesia of, in office, *1968*: Jan., 180
  - nerve blocks in, *1968*: Jan., 125
  - venous diseases, phlebography in, *1967*: Jan., **161-174**
- Leprosy, *1968*: July, 904
- Leriche syndrome, *1968*: Jan., 63
- Leucine tolerance test, in hypoglycemia, *1968*: March, 286-293
- Leukemia(s), acute, in treated polycythemia vera, *1966*: Nov., 1511
    - preleukemic, *1967*: July, 1051
    - promyelocytic, *1967*: July, 1054
    - smoldering, *1967*: July, 1053
    - variants, *1967*: July, **1051-1059**
  - antigens of, specific, *1966*: May, **901-912**
  - chromosomal alterations in, *1966*: May, 879
  - electron microscopy in, *1966*: May, 892
  - gastrointestinal bleeding in, *1966*: May, 749
  - granulocytic, acute, corticosteroids in, dangers, *1966*: Nov., **1653-1668**
    - chronic treatment, *1966*: May, 805
  - leukoerythroblastosis in, *1966*: May, 786
  - lymphocytic, chronic, lymphangiography in, *1967*: Jan., 239
  - mortality, *1966*: May, 618
  - oral lesions, *1966*: March, 367
  - platelet transfusions in, *1966*: Nov., 1564
  - vs. juvenile rheumatoid arthritis of acute onset, *1968*: May, 575
  - virus-like particles in, *1966*: May, 894
- Leukemoid reaction with normoblasts, *1966*: May, 779
- Leukocytes, polymorphonuclear, in rheumatoid arthritis inflammation, *1968*: May, 629
- Leukocytosis in liver disease, *1967*: July, 1005
  - in rheumatoid arthritis, *1968*: May, 543
    - juvenile, *1968*: May, 570
- Leukodystrophy, metachromatic, nerve biopsy in diagnosis, *1968*: July, 891
- Leukoerythroblastic anemia, clinical significance, *1966*: May, **779-790**
- Leukoerythroblastic reactions, *1966*: May, 779
- Leukoerythroblastosis, *1966*: May, 779
- Leukopenia, with rheumatoid arthritis, *1968*: May, 529
- Leukoplasia, oral, *1966*: March, 365
- Leukopoiesis, endocrine effects on, *1968*: March, 238-240
- Levocardia, types of transposition in, *1966*: Jan., 9
- Levophed. See *Norepinephrine.*
- Levoprome. See *Methotrimeprazine.*
- Levothyroxine, clinical uses, *1966*: Sept., 1393
- Levotriiodothyronine, clinical uses, *1966*: Sept., 1393
- Librium. See *Chlordiazepoxide, 1967*: Sept., 1250
- Lichen planus, oral, *1966*: March, 365

Lichenoid eruptions, drug, *1967*: July, 1076, 1082
Lidocaine, after myocardial infarction, *1968*: Sept., 1064
  for cardiac arrhythmias, *1967*: Sept., 1235
  for epidural anesthesia, *1968:* Jan., 212
  in office, *1968*: Jan., 175, 178
Light sensitivity. See *Photosensitivity.*
Lincomycin, for postoperative staphylococcal infections, *1966*: May, 798
  for staphylococcal pneumonia, *1967*: March, 544
  toxic reactions, *1967*: July, 929
Lipase, pancreatic, congenital absence, *1968*: Nov., 1275
Lipid(s), serum levels of, coronary artery disease and, *1967*: Jan., 127; *1968*: Sept., **1249-1260**
    control of, dietary, *1968*: Sept., 1252-1253
      drug, *1968*: Sept., 1253-1259
  thrombosis and, *1967*: Jan., 156
Lipodystrophy, intestinal, cutaneous melanosis with, *1966*: March, 351
Lipoproteins, blood, myocardial infarction and, *1968*: Sept., 1061
Liposarcoma, retroperitoneal, lymphangiography in, *1967*: Jan., 244
Liquids, deposition on mucosa, aerosol therapy for, *1967*: March, 313
Liver, biopsy, needle, *1968*: Nov., 1415
    percutaneous, *1966*: May, 756
    touch preparations, cytologic examination, *1966*: May, 756
  carcinoma, diagnosis, newer techniques, *1966*: May, 756
    unusual aspects, *1966*: May, 753
  cirrhosis. See *Cirrhosis.*
  disease(s), anemia, *1966*: March, **543-549**
    autoimmune, *1966*: March, 403
    classification, *1968*: Nov., 1415
    diagnostic procedures, *1968*: Nov., **1407-1416**
    evidence of, that may be overlooked, *1967*: July, **1003-1013**
    fibrinolysis in, with bleeding, *1967*: July, 1065, 1068
    in hypernephroma, *1966*: July, 1070
    in ulcerative colitis, *1966*: March, 531
    renal manifestations, *1966*: March, 512
    symposium on, *1968*: Nov., **1265-1501**
  dysfunction, constitutional, *1968*: Nov., 1420
  impairment, in congestive heart failure, *1966*: March, **487-493**
    in Graves' disease, *1967*: July, 922
    in sickle cell anemia, *1966*: Nov., 1525
    in thyroid disease, *1966*: March, 588
Liver (*Continued*)
  impairment, inflammation. See *Hepatitis.*
  physiology, implications of current research in, *1968*: Nov., 1403
  scanning, *1968*: Nov., 1412
    for cancer, *1966*: May, 695, 756
Loop of Henle, *1966*: July, 933
L-Thyroxine. See *Hormones, thyroid.*
L-Triiodothyronine. See also *Hormones, thyroid.*
  uptake test, *1968*: March, 468
Lucey-Driscoll syndrome, *1968*: Nov., 1421
Lumbosacral corset support, *1967*: Sept., 1338
Lundh test, in chronic pancreatitis, *1968*: Nov., 1491
Lung, abscess, from IPPB therapy, *1967*: March, 534
    metastatic, *1967*: March, 533
    primary, *1967*: March, 529
    with bronchial obstruction or stenosis, *1967*: March, 532
    with lobar pneumonia, *1967*: March, 531
  biopsy, in farmer's lung, *1967*: March, 480
  bird breeder's (fancier's), *1967*: March, 459, 477
  carcinoma, classification of patients, initial, *1967*: March, 550
    complications, *1967*: March, 564
      treatment, *1967*: March, 568
    diagnosis, cytologic, *1966*: May, 654
    extrathoracic manifestations, *1967*: July, **1041-1044**
    inoperable, management of patient, *1967*: March, **563-572**
    mortality, *1966*: May, 621
    prognosis and treatment, causes of defective statistics, *1967*: March, **549-562**
    survival rates, *1967*: March, 556
    therapeutic decisions, reason for, *1967*: March, 555
    treatment, index of accomplishment, *1967*: March, 356
  diseases, chronic, heart failure following, classification, *1966*: Jan., 39, 40
    iatrogenic, *1967*: March, 460, 478
    in rheumatoid arthritis, *1967*: July, 1022
    obstructive, chronic, aerosols and IPPB in, *1967*: March, 307-323
      prognosis in, *1967*: March, **363-371**
      rehabilitation in, *1967*: March, **349-361**
      respiratory failure in, *1967*: March, **323-340**

Lung (*Continued*)
  diseases, obstructive, surgical risk in, evaluation of, *1967*: March, **341-347**
    suppurative, *1967*: March, **529-540**
  farmer's, *1967*: March, **459-482**
  fibrosis, interstitial, diffuse, *1967*: March, **439-457**
  function, in heart disease, *1966*: Jan., **141-157**
    tests of, for changes in residual volume with IPPB, *1967*: March, 318
      for separation of dyspnea due to heart and lung disease, *1966*: Jan., 153
      in chronic obstructive disease, mortality in relation to, *1967*: March, **363-371**
      in diffuse interstitial pulmonary fibrosis, *1967*: March, 443, 451, 452, 454
      in farmer's lung, *1967*: March, 463, 464, 479
  fungal infections, recognition and management, *1967*: March, **519-527**
  granulomatoses, due to inhaled organic antigens, *1967*: March, **459-482**
  honeycomb, in diffuse interstitial pulmonary fibrosis, *1967*: March, 441
  infections, due to atypical mycobacteria, pathogenesis, clinical manifestations, and treatment, *1967*: March, **503-517**
    mycotic, recognition and management, *1967*: March, **519-527**
  involvement, in renal disease, *1966*: July, **1055-1066**
  lesions of, in rheumatoid arthritis, *1968*: May, 619
  oat-cell carcinoma, *1968*: March, 323
  purpura, with nephritis, *1966*: July, 1055
  sarcoidosis, clinical features and management, *1967*: March, **483-502**
  scanning, in pulmonary embolism, *1967*: Jan., 177, 180
  tuberculosis. See under *Tuberculosis.*
Lupus erythematosus, autoimmune, *1966*: March, 402
  light sensitivity in, *1966*: Sept., 1305
  systemic, antinuclear factor tests in, *1968*: May, 559
    chronic biologic false-positive test for syphilis in, *1966*: Sept., 1271, 1273
    cutaneous melanosis with, *1966*: March, 353
    gastrointestinal manifestations, *1966*: March, 419
    nephritis in, *1966*: July, **1119-1125**
    procaine-induced, *1966*: Sept., 1276
Lupus erythematosus (*Continued*)
  systemic, pulmonary and renal manifestations, *1966*: July, 1058
    synovianalysis in, *1966*: Sept., 1288, 1289
    vs. rheumatoid arthritis, *1968*: May, 560, 562
      juvenile, *1968*: May, 575
Lupus nephritis, diagnosis and treatment, *1966*: July, **1119-1125**
Lymph nodes, cancerous invasion of, dynamics, *1967*: Jan., 254
  evaluation, by lymphangiography, *1967*: Jan., 235
  filtering function, in cancer, *1967*: Jan., 254
  hyperplasia, in rheumatoid arthritis, *1968*: May, 619
  metastatic disease, lymphangiography in, *1967*: Jan., 236
Lymphadenitis, lymphangiography in, *1967*: Jan., 236
  tuberculous, *1966*: Sept., 1442
Lymphadenopathy, in rheumatoid arthritis, *1968*: May, 493
    juvenile, *1968*: May, 570
Lymphangiography, clinical aspects, *1967*: Jan., **227-248**
  indications, techniques, and complications, in lymphomas and carcinomas, *1966*: May, **675-688**
Lymphatic obstruction, lymphangiography in, *1967*: Jan., 240
Lymphatic system, function and anatomy, *1967*: Jan., 228
  malignant disease and, *1967*: Jan., **249-261**
  response to ionizing irradiation, *1967*: Jan., 249
Lymphedema, evaluation, by lymphangiography, *1967*: Jan., 231, 240
Lymphocytes, rôle, in malignant disease, *1967*: Jan., 255
Lymphoma(s), gastrointestinal bleeding in, *1966*: May, 749
  lymphangiography in, indications, techniques and complications, *1966*: May, **675-688**
  malignant, with splenomegaly and hypersplenism in elderly, splenectomy for, *1966*: Nov., 1538
  simulating benign gastrointestinal disease, *1966*: May, 749
Lymphopoiesis. See *Leukopoiesis.*
Lymphosarcoma, lymphangiography in, *1967*: Jan., 239, 244
Lysosomes, activities, *1968*: May, 635-637
  in pathogenesis of rheumatoid arthritis, *1968*: May, **635-641**

Lysosomes (*Continued*)
  in rheumatoid arthritis, *1968*: May, 626-628
  inflammation and, *1968*: May, 637

MACROGLOBULINEMIAS, monoclonal immunoglobulins in, *1966*: May, 670
Macula densa, *1966*: July, 933
Magnesium, concentration of, cardiovascular system and, *1968*: Sept., 1244
  imbalance, in renal failure, *1966*: July, 1181
Malabsorption, *1968*: Nov., **1339-1354**
  in thyrotoxicosis, *1966*: March, 583
  inheritance, *1968*: Nov., 1276
Malalignment of joints, in rheumatoid arthritis, *1968*: May, 660
Malaria, anemia, *1966*: Nov., 1708
  changing outlook, *1967*: May, **729-734**
Malingering, pathologic, *1968*: Jan., 156
Malnutrition, cholera and, *1967*: May, 648
  gastrointestinal disease and, *1968*: Nov., 1398
  in gluten enteropathy, *1966*: March, 521
  oral lesions, *1966*: March, 366
  polyneuropathy and, *1968*: Jan., 112
  shigellosis and, *1967*: May, 648
  weanling diarrhea and, *1967*: May, 643
Mannitol, for hypovolemic shock, *1967*: Jan., 95
  for oliguric renal failure, *1966*: July, **1159-1163**
  for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1149
  side effects, *1966*: July, 1161
Maple bark disease, *1967*: March, 459, 460, 477
Marfan's syndrome, *1967*: Jan., 199
  gastrointestinal manifestations and genetic factors, *1968*: Nov., 1277
Mastocytosis, systemic, cutaneous melanosis with, *1966*: March, 353
Mastodynia, oral contraceptive drugs and, *1967*: Sept., 1272
Maxipen, *1967*: Sept., 1108
Measles, encephalitis due to, corticosteroids in, *1967*: Sept., 1190
  gamma globulin in, *1965*: Nov., 1747
  German. See *Rubella.*
  neurologic complications, *1967*: May, 708
  vaccines, *1967*: May, **599-608**
    in infants and children, *1967*: May, 583, 605
    inactivated, *1967*: May, 602, 604
    live, *1967*: May, 599, 604
    protective effects, *1967*: May, 604
Median nerve, compression, *1968*: July, 778-779
Mediastinum, oat-cell carcinoma, *1968*: March, 323
Medicine, adolescent, *1967*: Nov., **1439-1451**
  internal. See *Internal medicine.*
Medionecrosis, cystic, and aneurysmal dilatation of ascending aorta, *1968*: Sept., **1145-1156**
Mediterranean fever, periodic, *1966*: March, 372, 373-377
Medroxyprogesterone, *1967*: Sept., 1263
Melanoma, malignant, fluorescein angiography of fundus in, *1968*: July, 863
Melanosis, cutaneous, gastrointestinal disorders with, *1966*: March, **347-602**
  oral, *1966*: March, 368
Melphalan, as anticancer agent, *1966*: May, 858, 863
  for multiple myeloma, *1966*: Nov., 1570
Meninges, irritation of, chronic renal failure and, *1968*: July, 848
Meningitis, H. influenzae, ampicillin in, *1967*: Sept., 1137
  tuberculous, *1966*: Sept., 1443
Meningococcal disease, sulfonamide-resistant, *1967*: May, **719-727**
Meningo-encephalitis. See also *Encephalitis.*
Menstruation, abnormal, psychologic aspects, *1967*: Nov., 1376
  acyclic, oral contraceptive drugs and, *1967*: Sept., 1269
  cessation, *1968*: March, **339-355.** See also *Amenorrhea.*
Mental illness, in adolescents, diagnosis, *1967*: Nov., 1447
  in aged, *1967*: Nov., 1518
    components of disorder and psychiatric treatment approaches. *1967*: Nov., 1523, 1525
    psychotherapy for, *1967*: Nov., 1522
    test for, *1967*: Nov., 1521
Mental symptoms in adrenocortical disease, *1967*: July, 886
Meperidine hydrochloride, for pain, in children, *1968*: Jan., 134
    in labor, *1968*: Jan., 140
Mephenesin (Tolserol), for trigeminal neuralgia, *1968*: July, 798
Mephentermine (Wyamine), for shock, *1968*: Sept., 1085
Mepivacaine, for epidural anesthesia, *1968*: Jan., 212
Meprobamate, for pain, *1968*: Jan., 51
6-Mercaptopurine, as anticancer agent, *1966*: May, 859, 864
  for chronic granulocytic leukemia, *1966*: May, 807

Mestranol, *1967*: Sept., 1263, 1271, 1272
Metabolism, acid-base, *1966*: May, 712
  carbohydrate, pregnancy and, *1968*: March, 253-257
  changes associated with recovery from vitamin B_{12} deficiency, *1966*: Nov., **1627-1641**
    rheumatoid arthritis and, *1968*: May, 601
  copper, Wilson's disease and, *1968*: July, **989-1001**
  creatine, myopathy and, *1968*: March, 247
  disorders, low back pain and, *1968*: Jan., 66
  immunoglobulin, *1966*: Nov., **1487-1499**
  iodide, pregnancy and, *1968*: March, 257
  laboratory tests of, thyroid therapy and, *1968*: March, 443
  potassium, myopathy and, *1968*: March, 249
  steroid, pregnancy and, *1968*: March, 259-261
  water and electrolyte, *1966*: May, 710
    abnormalities of, cerebral disorders and, *1968*: July, 846
Metaraminol (Aramine), for shock, *1967*: Jan., 79; *1968*: Sept., 1085
  sympathomimetic effects, *1967*: July, 984
Metatarsophalangeal joints, in rheumatoid arthritis, *1968*: May, 498
Methacycline for chronic bronchitis, *1967*: Sept., 1172
Methamphetamine (Desoxyn), for narcolepsy, *1968*: July, 782
Methetoin (Deltoin), for seizures, *1968*: July, 972
Methicillin, *1967*: Sept., 1109
  for bacterial endocarditis, *1968*: Sept., 1098
  for postoperative staphylococcal infections, *1966*: May, 797
  for staphylococcal infections, *1967*: March, 544
  toxic reactions, *1967*: July, 930
Methotrexate, as anticancer agent, *1966*: May, 859, 863
  for metastatic gastrointestinal cancer, *1966*: March, 429, 433
  for rheumatoid arthritis, *1967*: Sept., 1221; *1968*: May, 750, 754
Methotrimeprazine, analgesic properties, *1968*: Jan., 39
  for pain, *1968*: Jan., 50
Methoxamine (Vasoxyl), as aid to cardiac auscultation, *1966*: Jan., 83, 87
  for shock, *1967*: Jan., 71, 72; *1968*: Sept., 1085
Methoxamine (Vasoxyl) (*Continued*)
  sympathomimetic effects, *1967*: July, 984
Methyldopa (Aldomet), for hypertension, *1967*: Jan., 33, July, 986; *1968*: Sept., 1232
Methylhydrazine, as anticancer drug, *1966*: May, 867
  for Hodgkin's disease, *1966*: May, 828
Methylphenidate (Ritalin), for narcolepsy, *1968*: July, 782
  for orthostatic hypotension, *1968*: July, 814
Methylprednisone, for rheumatoid arthritis, *1968*: May, 743
Methyprylon, for pain, *1968*: Jan., 49
Metronidazole for alcoholism, *1967*: Sept., 1257
Metycaine. See *Piperocaine.*
Microscopy, electron, of cancer cells, *1966*: May, **887-900**
  of normal and diseased blood vessels, *1967*: Jan., **139-150**
Microthrombosis, disseminated, *1967*: Jan., 155
Milk-alkali syndrome, *1966*: March, 569
Miltown. See *Meprobamate.*
Mintezol, *1967*: Sept., 1206
Mitral insufficiency, causes of and surgery for, *1968*: Sept., 1116-1122
  phonocardiogram in, *1966*: Jan., 98
    after methoxamine, *1966*: Jan., 83
Mitral stenosis, lung function alterations in, *1966*: Jan., 154
  phonocardiogram, *1966*: Jan., 95
    after drugs, *1966*: Jan., 79
  pulmonary hypertension in, *1966*: Jan., 40
Mogadon. See *Nitrazepam.*
Monoamine oxidase inhibitors, as antidepressants, *1967*: Nov., 1460, 1462
  for hypertension, *1967*: July, 978, 980, 987
Mononucleosis, infectious, cold agglutinins in, *1966*: Nov., 1646
  diagnostic criteria, *1967*: May, 810
  in children, *1967*: May, 822
  neuropathy and, *1968*: July, 902
  vs. Guillain-Barré-Strohl syndrome, *1968*: July, 901
Monopar, *1967*: Sept., 1207
Morphine, for pain in children, *1968*: Jan., 134
  in labor, *1968*: Jan., 140
Morphine sulfate, for pain after myocardial infarction, *1968*: Sept., 1065
Motility, esophageal, implications of current research in, *1968*: Nov., 1269
Mouth, carcinoma, diagnosis, cytologic, *1966*: May, 658

Mouth (*Continued*)
  diseases, eight basic, *1966*: March, 363
  lesions, in systemic diseases, *1966*: March, **361-369**
Mucormycosis, pulmonary, *1967*: March, **519-527**
Mucosa, oral, *1966*: March, 361
Mucoviscidosis, adult, management, *1967*: March, 538
  inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
  pancreatic insufficiency in, *1966*: March, 452
Multiple endocrine adenomatosis, *1968*: March, 303
Mumps, neurologic complications, *1967*: May, 713
Murmurs, cardiac, *1966*: Sept., 1210-1217
    changes in intensity, following drug administration, *1966*: Jan., 78, 86
    classification, *1966*: Jan., 103
    in atrial septal defects, *1967*: July, 953
  tricuspid, *1966*: Sept., 1218
Muscles, abnormalities, chronic renal failure and, *1968*: July, 848-849
  diseases, ultrastructural reactions in, *1968*: July, **909-931**
      glycogen sequestration, *1968*: July, 926-928
      mitochondria, *1968*: July, 922-926
      Z disk, *1968*: July, 910-922
  wasting of, endocrine disorders and, *1968*: March, **243-252**
  weakness of, cervical root pain and, *1968*: July, 774
Muscle stretch reflex, cervical root pain and, *1968*: July, 775
Mushroom worker's disease, *1967*: March, 460, 478
Mustards, phenylalanine, in multiple myeloma, *1966*: Nov., 1570
Myasthenia gravis in Graves' disease, *1967*: July, 922
  speech disturbances in, *1968*: July, 839
Mycobacteria, atypical (anonymous), infections due to, pathogenesis, clinical manifestations, and treatment, *1967*: March, **503-517**
Mycoplasma hominis, *1967*: May, 793
Mycoplasma infections of animals, rheumatoid arthritis and, *1968*: May, 667-669, **677-686**
Mycoplasma pneumoniae, *1967*: May, 793
  infections due to, *1967*: May, 793-800, 813
  serologic tests, *1967*: May, 797
Mycoplasmas, rheumatoid arthritis and, *1968*: May, 675
Mycoplasmas (*Continued*)
  role in human respiratory disease, *1967*: May, **791-802**
  species, of man, *1967*: May, 791, 792
Mycoses, drugs in, toxic reactions, *1967*: July, 926
  pulmonary, recognition and management, *1967*: March, **519-527**
Mycostatin, *1967*: Sept., 1183
Myeloid metaplasia, in elderly, splenectomy for, *1966*: Nov., 1544
  leukoerythroblastosis in, *1966*: May, 787
  treatment, *1966*: May, 808
Myeloma, multiple, monoclonal immunoglobulins in, *1966*: May, 669
    neuropathy and, *1968*: July, 906
    renal failure in, *1967*: July, 997
    treatment, current concepts, *1966*: Nov., **1569-1578**
  plasmacytic. See *Myeloma, multiple.*
Myeloproliferative disorders, leukoerythroblastosis in, *1966*: May, 786
  management, *1966*: May, **803-817**
Myelosuppressive agents in polycythemia vera, *1966*: Nov., 1504
Myleran. See *Busulfan.*
Myocardiopathy, alcoholic, *1966*: Jan., 304; *1968*: Sept., **1183-1191**
Myocarditis, serum enzymes in, *1966*: Jan., 186
Myocardium, infarction, acute, management, *1968*: Sept., **1061-1075**
    arrhythmias and, propanolol for, *1968*: Sept., 1025
    blood lipoproteins and, *1968*: Sept., 1061
    complications of, surgery for, *1968*: Sept., **1115-1131**
    consequences, *1968*: Sept., 1063-1064
    ectopic configuration in, *1966*: Jan., 57
    etiology, *1968*: Sept., 1061-1062
    hyperbaric oxygen in, *1967*: Sept., 1311
    in coronary artery disease, *1967*: July, 942, 944
    postoperative chest pain and, *1968*: Jan., 91, 98
    prodromata, *1968*: Sept., 1062-1063
    serum enzymes in, *1966*: Jan., **171-191**
    shock in, treatment, physiologic basis, *1967*: Jan., **69-81**
  injury, serum lactic dehydrogenase in diagnosis, *1966*: Jan., **193-209**
  oxygen demands of, propanolol and, *1968*: Sept., 1032
  tumors, metastatic, *1966*: May, 737
Myochrysine. See *Gold thiomalate.*

Myoglobulinuria, renal failure in, *1967*: July, 997
Myopathy(ies). See also *Muscle(s).*
  steroid, *1968*: March, 245-246
    biochemical mechanisms, *1968*: March, 249
  thyrotoxic, chronic, *1967*: July, 921; *1968*: March, 243-245
Myositis, in rheumatoid arthritis, *1968*: May, 619
Myxedema. See also *Hypothyroidism.*
  gastrointestinal manifestations, *1966*: March, 586
  parietal cell antibody and, *1968*: Nov., 1286
  pretibial, in Graves' disease, *1967*: July, 917
  thyroid hormones in, *1966*: Sept., 1395, 1397
  treatment, *1968*: March, **431-450**
    evaluation, *1968*: March, 441
Myxedema coma, *1968*: March, 445

NAFCILLIN, *1967*: Sept., 1111
  for staphylococcal postoperative, infections, *1966*: May, 797
Nalidixic acid, *1967*: Sept., 1128-1131, 1143
  toxic reactions, *1967*: July, 934
Nalline. See *Nalorphine.*
Nalorphine, analgesic properties, *1968*: Jan., 38
Narcolepsy, treatment, *1968*: July, **781-787**
Narcotics, dependence on, *1968*: Jan., 33-36
  duration of action, *1968*: Jan., 42
  for pain, *1968*: Jan., **33-34**
    postoperative, *1968*: Jan., 85
  in children, *1968*: Jan., 132
  in labor, *1968*: Jan., 140
  oral administration, *1968*: Jan., 41
  potency and efficacy, *1968*: Jan., 39
  regulations for use, *1968*: Jan., 36
  selection, *1968*: Jan., 39-44
Nasal cavity, topical analgesia, *1968*: Jan., 178
Nasogastric suction, for pyloric obstruction, *1968*: Nov., 1333
Nasopharyngeal cultures in management of infections, *1966*: Sept., 1424
Nasopharyngitis, acute, in adults, *1967*: May, 807, 809
    in children, *1967*: May, 821
Natulan, for Hodgkin's disease, *1966*: Nov., 1607
Natural childbirth, *1968*: Jan., 145
Neck, injuries to, flexion-extension, *1968*: July, 775
    restricted movement, *1968*: July, 774
Necrolysis, epidermal, toxic, *1967*: July, 1076, 1080
Neomycin, for hypercholesterolemia, *1968*: Sept., 1255
  toxic reactions, *1967*: July, 934
Neo-Synephrine. See *Phenylephrine.*
Neoplasm(s). See *Carcinoma, Tumors,* etc.
Nephritis, glomerular. See *Glomerulonephritis.*
  interstitial, due to phenacetin, *1966*: July, 1085
  lung purpura with, *1966*: July, 1055
  lupus, diagnosis and treatment, *1966*: July, **1119-1125**
  radiation, *1966*: July, 969, 973, 974
Nephrocalcinosis, drugs causing, *1966*: March, 570
Nephrolithiasis in hyperparathyroidism, *1967*: July, 879
Nephron, structure, *1966*: July, **927-935**
Nephropathy. See *Kidney, diseases.*
Nephrosclerosis, arteriograms in, *1967*: Jan., 65, 67
Nephrotic syndrome, gastrointestinal manifestations, *1966*: March, 508
  in constrictive pericarditis, *1966*: Jan., 260
Nephrotomography in kidney disease, *1966*: July, **957-967**
Nephrotoxins, *1966*: March, 507
Nerves, biopsy, *1968*: July, **885-893**
  blocks, in treatment of pain in extremities, *1968*: Jan., **123-129**
  cranial, chronic renal failure and, *1968*: July, 847
    pain originating in, *1968*: Jan., 111
    pain transmission in, *1968*: Jan., 18
  optic, lesions of, pupillary reflexes in, *1968*: July, 877
  peripheral, bony tunnel syndromes and, *1968*: Jan., 113
    diseases of. See *Neuropathy, peripheral.*
    pain originating in, *1968*: Jan., 112
    pain reception and, *1968*: Jan., 15
    trauma to, *1968*: Jan., 113
  spinal, pain transmission in, *1968*: Jan., 16
    root lesions, *1968*: Jan., 114
Nervous system, autonomic, hypertension and, *1967*: July, 977
    renin-angiotensin system and, *1968*: March, 275
  central, disease of, pituitary function and, *1968*: March, **357-369**
    enterovirus infections, *1967*: May, **681-692**
    schistosomiasis, *1966*: March, 597-602
  disorders, motor speech signs in, *1968*: July, **835-844**

Nervous system (*Continued*)
  disorders, orthostatic hypotension and, *1968*: July, 812, 813
    pupil in, *1968*: July, **871-884**
    symposium on, *1968*: July, **771-1001**
    vs. inappropriate secretion of antidiuretic hormone, *1968*: July, 824
  pain originating in, *1968*: Jan., **111-121**
    neurolytic substances for, *1968*: Jan., 164
  peripheral, chronic renal failure and, *1968*: July, 847-848
  sympathetic, adrenergic receptor blockers and, *1968*: Sept., **1049-1060**
Nethalide (Alderlin), blocking action, *1968*: Sept., 1011
Neuralgia, postherpetic, *1968*: Jan., 115
    percutaneous cordotomy for pain in, *1968*: Jan., 196
    radiation therapy for pain of, *1968*: Jan., 204
  post-traumatic, percutaneous cordotomy for, *1968*: Jan., 197
  trigeminal, *1968*: Jan., 111
    medical treatment, *1968*: July, **797-800**
Neuritis, brachial, paralytic, *1968*: July, 776-777
  febrile, acute, *1968*: July, 901
  shoulder girdle, *1968*: July, 776-777
Neurofibromatosis, cutaneous melanosis with, *1966*: March, 356
  inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Neurohumors, in regulation of adenohypophyseal hormone secretion, *1968*: March, 357
Neurologic complications of infectious diseases, *1967*: May, **701-717**
Neurologic disorders, secondary hypertension and, *1968*: Sept., 1214
Neurolytic agents, for pain, *1968*: Jan., **161-171**
    techniques of administering, *1968*: Jan., 168
Neuroma, of eighth cranial nerve, cerebellopontine angle syndrome and, *1968*: July, 789, 791
Neuromuscular disorders, alveolar hypoventilation in, *1967*: March, 416
  hypoventilation, *1966*: Jan., 46
Neuropathy, carcinomatous sensory, *1968*: July, 900
  Charcot-Marie-Tooth type, *1968*: July, 903
  diabetic, *1966*: March, **565-568**
  congenital sensory, *1968*: July, 899
  Dejerine-Sottas type, *1968*: July, 903
  hereditary sensory radicular, *1968*: July, 899
Neuropathy (*Continued*)
  hypertrophic, *1968*: July, 903
  ischemic, *1968*: July, 905
  optic, in Graves' disease, *1967*: July, 919
  peripheral, causes, *1968*: July, 896
    diagnosis and classification, *1968*: July, **895-908**
    dorsal root ganglion cell type, *1968*: July, 899-900
    in hypernephroma, *1966*: July, 1076
    in rheumatoid arthritis, *1967*: July, 1023
    symptoms, *1968*: July, 895
    with predominantly motor symptoms, *1968*: July, 900-904
    with predominantly sensory symptoms, *1968*: July, 904-906
  Refsum type, *1968*: July, 904
Neutrophils, in rheumatoid arthritis inflammation, *1968*: May, 629
Newborn. See under *Infants.*
Nicotinic acid, deficiency, oral lesions, *1966*: March, 366
  for hypercholesterolemia, *1968*: Sept., 1258
Nitrazepam (Mogadon), for seizures, *1968*: July, 972
Nitrofurantoin, neurologic side effects, *1968*: July, 850
  toxic reactions, *1967*: July, 934
Nitrogen mustard, as anticancer agent, *1966*: May, 858, 862
  for Hodgkin's disease, *1966*: May, 827, Nov., 1606
  for rheumatoid arthritis, *1967*: Sept., 1220; *1968*: May, 696, 750
Nitrogen retention, in renal failure, *1966*: July, 1176
Nitrous oxide analgesia, in labor, *1968*: Jan., 141
N-methylhydrazine, for Hodgkin's disease, *1966*: Nov., 1607
Nocardial infections, pulmonary, *1967*: March, **519-527**
Nodules, subcutaneous, in rheumatoid arthritis, *1968*: May, 493
Noludar. See *Methyprylon.*
Norepinephrine, adrenergic receptors and, *1968*: Sept., 1010
  for shock, *1967*: Jan., 71, 73, 76, 78, 94; *1968*: Sept., 1084
  sympathomimetic effects, *1967*: July, 983
Norethindrone, *1967*: Sept., 1263, 1271
Norethynodrel, *1967*: Sept., 1263
Norinyl, *1967*: Sept., 1263
Norlestrin, *1967*: Sept., 1263
Novobiocin, toxic reactions, *1967*: July, 929
Novocaine. See *Procaine.*

NP-Lx test, for antinuclear factors, *1968*: May, 561
Nucleus pulposus, herniated, sciatica and, *1968*: Jan., 184
Nutrition, clinical, gastrointestinal disease and, *1968*: Nov., **1397-1402**
  deficiencies. See also *Malnutrition.*
    amenorrhea and, *1968*: March, 341
    oral lesions, *1966*: March, 366
  for pyloric obstruction, *1968*: Nov., 1334
  in congestive heart failure, *1966*: Jan., **301-307**
  influence on enteric infections, *1967*: May, **643-652**
Nutritional megaloblastic anemias, etiologic considerations, *1966*: Sept., **1245-1256**
Nystatin, topical, for fungus infections, *1967*: Sept., 1183

OBESITY, amenorrhea and, *1968*: March, 342
  as coronary risk factor, *1966*: Jan., 238
  cardiovascular disease and, *1964*: Sept., 1190; *1966*: Jan., 302
  diabetes and, *1966*: Sept., 1372
  hypoventilation, *1966*: Jan., 47
  in adrenocortical disease, *1967*: July, 885
  thyroid hormones in, *1966*: Sept., 1398
Obsessive-compulsive reactions, internist's role, *1967*: Nov., 1418
Obstetrician, psychiatry for, *1967*: Nov., **1375-1380**
Ointments, sun-protective, *1966*: Sept., 1309
Oligomenorrhea, oral contraceptive drugs and, *1967*: Sept., 1271
Oliguria, in poststreptococcal acute glomerulonephritis in children, *1966*: July, 1143, 1148
  in renal failure, use of mannitol in, *1966*: July, **1159-1163**
  secondary to congestive heart failure, *1966*: Jan., 258
Omnicillin, *1967*: Sept., 1128
Onycholysis, in Graves' disease, *1967*: July, 917
Oophorectomy, in carcinoma of breast, *1966*: Sept., 1460
    prophylactic vs. therapeutic, *1966*: Sept., 1460
o,p′-DDD as anticancer drug, *1966*: May, 867, Sept., 1462
Ophthalmoplegia, in Graves' disease, *1967*: July, 919
Optic nerve, lesions, pupillary reflexes in, *1968*: July, 877
Oracon, *1967*: Sept., 1263
Oral cavity, topical analgesia, *1968*: Jan., 178
Orbit, decompression of, in progressive exophthalmos, *1968*: March, **399-407**
Organomercurial diuretics, for refractory heart failure, *1968*: Sept., 1167
Orinase. See *Tolbutamide.*
Oropharyngeal cultures for management of infections, *1966*: Sept., 1424
Oroya fever, anemia of, *1966*: Nov., 1708
Ortho-Novum, *1967*: Sept., 1263
Orthopedic surgery, for rheumatoid arthritis, *1968*: May, **717-731**
Orthostatic hypotension, *1968*: July, **809-816**
Osmotic fragility in diagnosis of anemias, *1966*: Nov., 1700
Ospolot. See *Sulthiame.*
Osteitis fibrosa cystica in hyperparathyroidism, *1967*: July, 877
Osteoarthritis, hand in, *1968*: May, 495
  of synovial joints of spine, low back pain and, *1968*: Jan., 62
  synovianalysis in, *1966*: Sept., 1287, 1288
Osteoarthropathy, in lung cancer, *1967*: July, 1043
    treatment, *1967*: March, 570
Osteoarthrosis, secondary, in rheumatoid arthritis, *1968*: May, 663
Osteomalacia in gluten enteropathy, *1966*: March, 523
Osteomyelitis, chronic, hyperbaric oxygen in, *1967*: Sept., 1311
  vertebral, low back pain and, *1968*: Jan., 63
Osteoporosis, in adrenocortical disease, *1967*: July, 887
  in rheumatoid arthritis, *1968*: May, 656
  low back pain and, *1968*: Jan., 66
  post-traumatic, *1968*: Jan., 153
Ostium primum and secundum defects, atrial septum, in adults, *1966*: Jan., 19, 21
Otitis media, *1967*: May, 821
Ovarian hyperthecosis syndrome, *1968*: March, 345
Ovary(ies) carcinoma, advanced, management, *1966*: May, **845-856**
    diagnosis, cytologic, *1966*: May, 653
    mortality, *1966*: May, 626
    radiation therapy for pain of, *1968*: Jan., 206
  chromophobe adenoma and, *1968*: July, 830
  disorders of, amenorrhea and, *1968*: March, 345
  steroid synthesis by, *1967*: July, **903-913**
  tumors of, amenorrhea and, *1968*: March, 345

Ovulen, *1967*: Sept., 1263
Oxacillin, *1967*: Sept., 1110
  for bacterial endocarditis, *1968*: Sept., 1098
  for staphylococcal infections, postoperative, *1966*: May, 797
Oxazolidinediones, for seizures, *1968*: July, 963
Oxygen, hyperbaric, rationale and clinical uses, *1967*: Sept., **1301-1314**
Oxygen therapy, in acute respiratory failure, *1967*: March, 329
  after myocardial infarction, *1968*: Sept., 1066
  for status asthmaticus, *1967*: March, 381
Oxytetracycline, toxic reactions, *1967*: July, 937

PACEMAKERS, cardiac, clinical and physiologic studies, *1966*: Jan., **322-341**
    for slow ventricular rate, *1968*: Sept., 1070
Paget's disease, low back pain and, *1968*: Jan., 67
Pain, abdominal, acute intermittent porphyria and, *1968*: Nov., 1277
    diagnosis, *1966*: March, **439-447**
    diffuse angiokeratoma of Fabry and, *1968*: Nov., 1277
    in hyperthyroidism, *1966*: March, 585
  and its clinical management, symposium on, *1968*: Jan., **1-224**
  asymbolia for, *1968*: Jan., 117
  brachial, neurologic disorders and, *1968*: **773-779**
  cervical root, *1968*: July, 773-776
  chest, serum lactic dehydrogenase elevations with, *1966*: Jan., 202
  distribution, in cervical root syndrome, *1967*: July, 1029
  epidural anesthesia for, *1968*: Jan., **209-215**
  experimental, production of, *1968*: Jan., 27
    vs. pathologic, *1968*: Jan., 23
  hypnosis for relief of, *1968*: Jan., **217-224**
  in children, *1967*: Nov., 1434
    relief of, *1968*: Jan., **131-136**
  in extremities, differential neural blockade for, *1968*: Jan., **123-129**
  in liver disease, *1967*: July, 1004
  in pregnancy and labor, relief of, *1968*: Jan., **137-146**
  insensitivity to, congenital, *1968*: July, 899
  low back, *1968*: Jan., **55-71**
  measurement of, clinical, *1968*: Jan., **23-32**

Pain (*Continued*)
  narcotics for, *1968*: Jan., **33-45**
  neurologic substance of, *1968*: Jan., **111-121**
  neurolytic agents in relief of, *1968*: Jan., **161-171**
  patterns of, classic, *1968*: Jan., 104-108
  phantom limb, *1968*: Jan., 118
  postoperative, factors in, *1968*: Jan., 82
    in chest, *1968*: Jan., **91-101**
    in children, *1968*: Jan., 133
    incisional, *1968*: Jan., 108
    prevention of, *1968*: Jan., **73-80**
    reactions to, *1968*: Jan., 74
    treatment, *1968*: Jan., **81-90**
  radiation therapy, *1968*: Jan., **203-207**
  reception, peripheral, *1968*: Jan., 15
  receptors, stimulation of, *1968*: Jan., 6
  relief, in office, *1968*: Jan., **173-181**
  sedatives and tranquilizers for, *1968*: Jan., **47-53**
  stimulation of, *1968*: Jan., 3-4
  surgical diseases and, *1968*: Jan., **103-109**
  sympathectomy for relief of, *1968*: Jan., **147-159**
  sympathetic vs. somatic, nerve blocks and, *1968*: Jan., 123
  thalamic, *1968*: Jan., 116
  transmission and central projection of, *1968*: Jan., **15-21**
Palpation of precordium, *1966*: Sept., 1206
Palsy. See *Paralysis.*
Pancreas, carcinoma, diagnosis, newer techniques, *1966*: May, 658
    gastrointestinal bleeding in, *1966*: May, 748
    mortality, *1966*: May, 617
    radiation therapy for, *1968*: Jan., 205
    systemic effects, *1966*: March, 457
  cystic fibrosis, inheritance, *1968*: Nov., 1278
  diseases, autoimmune, *1966*: March, 404
    diagnostic tests, *1968*: Nov., **1483-1492**
    exocrine-endocrine deficiency in, *1966*: March, 454
    hypercalcemia and, *1966*: March, 571
    pain pattern in, *1968*: Jan., 106
    systemic manifestations, *1966*: March, 454
  hormones, influence on renal function, *1966*: July, 993
  insufficiency, in mucoviscidosis, *1966*: March, 452
  islet cells, histochemical characteristics, *1968*: March, 296
    hyperplasia of, *1968*: March, 299
    tumors. See also *Glucagonoma; Insulinoma.*

Pancreas (*Continued*)
  islet cells, tumors, endocrine syndromes with, *1968*: March, **295-312**
    hormone overproduction by, *1968*: March, 304-309
    laboratory tests for, *1968*: March, **283-294**
    systemic manifestations, *1966*: March, 455
    Zollinger-Ellison syndrome and, *1966*: March, 476; *1968*: March, 301
  systemic disease and, *1966*: March, **449-460**
Pancreatitis, acute, diagnostic tests, *1968*: Nov., 1483
    hyperlipemia and, *1968*: Nov., **1493-1501**
    peripheral effects, *1966*: March, 457
  chronic, diagnostic tests, *1968*: Nov., 1487
    relapsing, pancreatic exocrine-endocrine insufficiency in, *1966*: March, 454
  drug-induced, *1966*: March, 453
  hereditary, pancreatic exocrine-endocrine insufficiency in, *1966*: March, 455
  hyperlipemia in, *1966*: March, 450
  in hyperparathyroidism, *1966*: March, 450, Sept., **1403-1418**
  in renal failure, *1966*: March, 510
  radiation therapy for, *1968*: Jan., 204
Panic states in adolescents, *1967*: Nov., 1445
Pannus, formation of, rheumatoid arthritis and, *1968*: May, 611
Papillary muscle, dysfunction, after myocardial infarction, *1968*: Sept., 1074
    surgery for, *1968*: Sept., 1116
  rupture, surgery for, *1968*: Sept., 1119
Papilledema, fluorescein angiography of fundus in, *1968*: July, 860
Para-aminosalicylic acid in tuberculosis of kidney, *1966*: July, 1138
Parainfluenza virus, *1967*: May, 825
  infections, in adults, *1967*: May, 811
    in children, *1967*: May, 822, 823, 825
Paralysis, ascending, acute, *1968*: July, 901
  bulbar, speech disturbances in, *1968*: July, 838-841
  Landry's, *1968*: July, 901
  periodic, *1966*: March, 371
    in hyperthyroidism, *1967*: July, 922
  pseudobulbar, speech disturbances in, *1968*: July, 838-841
Paranoid reaction, internist's role, *1967*: Nov., 1421
Parathyroid disease, gastrointestinal manifestations, *1966*: March, 571
Parathyroid hormone, influence on renal function, *1966*: July, 991
  production, in nonendocrine cancer, *1966*: May, 772
Parents of adolescents, *1965*: March, 310; *1967*: Nov., 1440
Paresthesia, in fingers, *1968*: July, 774
    thoracic outlet syndromes and, *1968*: July, 777
Pargyline hydrochloride in hypertension, *1967*: Jan., 34
Parkinsonism, speech disturbances in, *1968*: July, 838-842
Parotitis. See also *Mumps.*
  staphylococcal, in renal failure, *1966*: March, 509
  surgical, radiation therapy for, *1968*: Jan., 204
PBI. See *Iodine, protein-bound.*
Pediatricians, child psychiatry training of, *1967*: Nov., **1427-1438**
Pellagra, neuropathy and, *1968*: July, 904
Pelvis, examination of, in amenorrhea, *1968*: March, 348
Pelvospondylitis ossificans. See *Spondylitis, ankylosing.*
Pemphigus, oral lesions, treatment, *1966*: March, 364
Penbritin, *1967*: Sept., 1113, 1128
Penicillin, for bacterial endocarditis, *1968*: 1098
  for pneumococcal pneumonia, *1967*: March, 542
  for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1148
  for pulmonary mycoses, *1967*: March, 524
  for sore throat, *1967*: May, 810
  natural, *1967*: Sept., 1107
  new, *1967*: Sept., **1107-1126**
  phenoxylethyl, *1967*: Sept., 1108
  semisynthetic, *1967*: Sept., 1108, 1116
    for postoperative staphylococcal ininfections, *1966*: May, 797
  toxic reactions, *1967*: July, 929, Sept., 1122
Penicillin G, for staphylococcal infections, *1967*: March, 544
  toxic reactions, *1967*: July, 929
Pentagastrin test, of gastric secretion, *1968*: Nov., 1308
Pentazocine, analgesic properties of, *1968*: Jan., 39
Peptic ulcer, diathesis, in Zollinger-Ellison syndrome, *1966*: March, 476
  disaccharidase deficiency and, *1968*: Nov., 1362
  gastric secretion and, *1968*: Nov., 1305
  hyperparathyroidism and, *1966*: March, 571
  in emphysema, *1967*: July, 1046

Peptic ulcer (*Continued*)
  in hyperparathyroidism, *1966*: Sept., **1403-1418;** *1967*: July, 879
  lesions associated with, *1966*: Sept., 1450
  multiple endocrine adenomatosis and, *1968*: Nov., 1278
  posterior, penetrating, syndrome of, *1966*: March, **461-468**
  pulmonary emphysema associated with, *1966*: March, **479-486**
  stress, etiology, diagnosis and treatment, *1966*: Sept., **1447-1455**
  thyroid disease and, *1966*: March, 582
Percussion of heart, *1966*: Sept., 1208
  jumping technique, *1966*: Sept., 1208, 1209
Pericarditis, constrictive (restrictive), *1966*: Sept., **1231-1244**
    nephrotic syndrome in, *1966*: Jan., 260
  serum enzymes in, *1966*: Jan., 186
  tuberculous, *1966*: Sept., 1444
  uremic, and cardiac tamponade, *1968*: Sept., 1237-1241
Pericardium, tumors, metastatic, *1966*: May, 737
    tamponade due to, *1966*: May, 738
Periodic disease, *1966*: March, **371-378**
Periosteum, bone formation at, hyperthyroidism and, *1968*: March, **393-398**
    rheumatoid arthritis and, *1968*: May, 663
Peritoneal dialysis. See *Dialysis, peritoneal.*
Peritoneoscopy for diagnosis of liver cancer, *1966*: May, 757
Peritonitis, paroxysmal, benign, *1966*: March, 373
  periodic, vs. juvenile rheumatoid arthritis of acute onset, *1968*: May, 575
  treatment failures, plan of management, *1966*: March, **551-563**
  tuberculosis, *1966*: Sept., 1444
Pernicious anemia. See under *Anemia.*
Personality, development, in child, *1967*: Nov., 1435
  disorders, in adolescents, *1967*: Nov., 1449
    internist's role, *1967*: Nov., 1418
Personality-behavior pattern as coronary risk factor, *1966*: Jan., 241
Pertussis, vaccination, encephalitis following, *1967*: May, 708
Peutz-Jeghers syndrome, *1966*: March, 386
  cutaneous melanosis with, *1966*: March, 354
  inheritance of, *1968*: Nov., 1274
Phalen's maneuver, *1968*: July, 778
Phantom limb, pain of, *1968*: Jan., 118
Pharyngitis, acute, causes and treatment, *1967*: May, 810
Pharyngotonsillitis, acute, *1967*: May, 810
Pharynx, topical analgesia of, *1968*: Jan., 178
Phenacetin, nephropathies due to, *1966*: July, **1085-1090**
Phenergan. See *Promethazine.*
Phenethicillin, *1967*: Sept., 1108
Phenformin in diabetes, *1966*: Sept., 1376, 1378
Phenobarbital sodium, for status epilepticus, *1968*: July, 968
Phenol, as neurolytic agent, *1968*: Jan., 163
Phenothiazines, as tranquilizers, *1967*: Nov., 1456
  photosensitivity due to, *1966*: Sept., 1300
  toxicity, *1967*: Nov., 1458
Phenoxybenzamine (Dibenzyline), blocking action of, *1968*: Sept., 1011
  for hypertension, *1967*: July, 991; *1968*: Sept., 1229
  for hypovolemic shock, *1967*: Jan., 93, 94
Phenoxylethyl penicillin, *1967*: Sept., 1108
Phentolamine (Regitine), blocking action of, *1968*: Sept., 1011
  for hypertension, *1967*: July, 991
  for hypovolemic shock, *1967*: Jan., 94
Phentolamine test, for pheochromocytoma, *1968*: Sept., 1219
Phenylalanine mustards, for multiple myeloma, *1966*: Nov., 1570
Phenylbutazone, for rheumatoid arthritis, *1968*: May, 694
  site of action of, *1968*: Jan., 8
Phenylephrine (Neo-Synephrine), for shock, *1968*: Sept., 1085
  sympathomimetic effects, *1967*: July, 983
Pheochromocytoma, adrenergic receptor blockers and, *1968*: Sept., 1044
  cardiac arrhythmias and, propanolol for, *1968*: Sept., 1026
  cardiac effects, *1966*: May, 740
  diagnosis, *1967*: Jan., 19
  hypertension and, *1968*: Sept., 1219
  hypertension due to, *1966*: Jan., 293; *1967*: July, 971
  treatment of, *1968*: Sept., 1229
Phlebography, in acute thrombophlebitis, *1967*: Jan., 163
  in postphlebitic syndrome, *1967*: Jan., 166
  in venous diseases of legs, *1967*: Jan., **161-174**

Phlebotomy, in hemochromatosis (iron storage disease), *1966*: Nov., **1579-1590**
  in polycythemia vera, *1966*: Nov., 1504
Phobias, internist's role, *1967*: Nov., 1418
Phonocardiography, auscultation and, relationship, *1966*: Jan., 91
  in cardiac diagnosis, *1966*: Jan., **91-109**
Phosphates, excretion, hyperparathyroidism and, *1968*: March, 454
Phosphorus, imbalance, in renal failure, *1966*: July, 1180
  radioactive, in chronic granulocytic leukemia, *1966*: May, 805
    in diagnosis of gastric cancer, *1966*: May, 755
    in polycythemia vera, *1966*: Nov., 1504
  serum, hypersomatotropism and, *1968*: March, 371
    hyperparathyroidism and, *1968*: March, 453
  tubular reabsorption, hyperparathyroidism and, *1968*: March, 455
Photoallergy, *1966*: Sept., 1298
Photodermatitis, from furocoumarins, *1966*: Sept., 1301
  from topical agents, *1966*: Sept., 1301
Photoscanning, renal, *1966*: July, 947-954
Photosensitivity, *1966*: Sept., **1295-1311**; *1967*: July, 1077, 1086
  due to furocoumarins, *1966*: Sept., 1301
    to internally administered compounds, *1966*: Sept., 1299
    to topical agents, *1966*: Sept., 1301
  management, *1966*: Sept., 1308
  polymorphous, *1966*: Sept., 1307
Phototoxicity, *1966*: Sept., 1298; *1967*: July, 1086
Phycomycosis, pulmonary, *1967*: March, **519-527**
Physical examination, in amenorrhea, *1968*: March, 348
  in hypertensive disease, *1967*: Jan., 17
  in rheumatoid arthritis, *1968*: May, 494
Physical therapy, for rheumatoid arthritis, *1968*: May, 701, **707-716**
Physician, nonpsychiatric, courses in basic psychiatry for, *1967*: Nov., **1493-1497**
      content and management, *1967*: Nov., **1499-1506**
    how the clinical psychologist can help, *1967*: Nov., **1477-1483**
    psychiatry for, symposium on, *1967*: Nov., **1361-1527**
  practicing, postgraduate education in psychiatry for, *1967*: Nov., **1363-1374**
Physician-patient relationship, effect on patient's role, *1967*: Nov., 1513
  in chronic illness, *1967*: Nov., 1406

Physician-patient relationship *(Continued)*
  in geriatrics, *1967*: Nov., 1516
Pigeon breeder's lung, *1967*: March, 459, 460, 477
Pigmentation, disorders of, in gastrointestinal disease, *1966*: March, **347-602**
    oral, *1966*: March, 368
Pinworm infestation, newer drugs in, *1967*: Sept., **1203-1211**
Pipazethate in chronic bronchitis, *1967*: Sept., 1176
Piperazine in pinworm infestation, *1967*: Sept., 1205, 1208
Piperocaine, for epidural anesthesia, *1968*: Jan., 212
Pituitary gland, amenorrhea and, *1968*: March, 342
  Crooke cell of, *1968*: March, 320
  function, central nervous system disease and, *1968*: March, **357-369**
    radiation suppression of, *1968*: Jan., 206
  hormones, influence on renal function, *1966*: July, 985
  tumors. See also *Chromophobe adenoma.*
    pathophysiology, *1968*: March, 321
    treatment, *1968*: March, 324
Placidyl. See *Ethchlorvynol.*
Plaquenil. See *Hydroxychloroquine.*
Plasma, clot lysis time, test for, *1967*: July, 1067
  for coagulation defects, *1967*: Sept., 1242
  for hypovolemic shock, *1967*: Jan., 91
  platelet-rich, for transfusion, *1966*: Nov., 1560
Plasminogen, activation of, *1967*: July, 1062
Platelets, function, *1966*: Sept., 1264
  preparations, *1966*: Nov., 1559
  survival, factors affecting, *1966*: Nov., 1565
  transfusion, in coagulation defects, *1967*: Sept., 1243
    use of, *1966*: Nov., **1559-1568**
Pleural effusion, in liver disease, *1967*: July, 1009
  in lung cancer, treatment, *1967*: March, 569
  tuberculous, *1966*: Sept., 1444
Pleuropneumonia-like organisms under electron microscope, *1966*: May, 896
Pneumococcal pneumonia, treatment, *1967*: March, 542
Pneumonia(s), atypical, primary, *1967*: May, 793-800
    in children, *1967*: May, 825
  bacterial treatment, *1967*: March, **541-548**

Pneumonia(s) (*Continued*)
  following renal transplantation, *1966*: July, 1057
  in children, *1967*: May, 824
  Klebsiella (Friedländer), treatment, *1967*: March, 545
  lobar, lung abscess with, *1967*: March, 531
  pneumococcal, treatment, *1967*: March, 542
  staphylococcal, penicillins in, *1967*: Sept., 1116
    treatment, *1967*: March, 543
  viral, *1967*: May, 793-800, 812
    in children, *1967*: May, 825
Pneumonitis, granulomatous, diffuse, due to inhaled antigens, *1967*: March, **459-482**
  uremic, *1966*: July, 106
  viral, *1967*: May, 812
Poisoning, arsenical, neuropathy and, *1968*: Jan., 112, July, 905
Poliodystrophy, progressive, inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Poliomyelitis, immunization, *1967*: May, **681-692**
Polyarteritis nodosa, gastrointestinal syndromes, *1966*: March, 420
  lung involvement in, *1966*: July, 845, 846, 1058
  renal manifestations, *1966*: July, 1058
Polyarthritis, benign, *1968*: May, 488
  peripheral, with ulcerative colitis, *1968*: May, 508
Polycillin, *1967*: Sept., 1113, 1128
Polycystic renal disease, congenital, pathogenesis, diagnosis and treatment, *1966*: July, **1101-1117**
Polycythemia vera, differential diagnosis, *1966*: Nov., 1501
  leukoerythroblastosis in, *1966*: May, 786
  treatment, *1966*: May, 808, Nov., **1501-1518**
  vs. hypernephroma, *1966*: July, 1070
Polymyositis, gastrointestinal manifestations, *1966*: March, 419
  vs. rheumatoid arthritis, *1965*: Jan., 91
Polymyxin B, toxicity, *1967*: July, 932
  vs. colistin, *1967*: Sept., 1134
Polymyxin E, *1967*: Sept., 1133
Polyneuritis, infective, acute, *1968*: July, 901
Polyneuropathies, *1968*: Jan., 112
  chronic, *1968*: July, 902
Polyps, of colon, discrete and occasional, *1966*: March, 388
    familial, inheritance, *1966*: March, **379-392;** *1968*: Nov., 1274
      management, *1966*: March, 389
Polyradiculoneuropathy, infectious, *1968*: July, 901
Polyradiculopathy, *1968*: Jan., 115
Polyserositis, periodic, *1966*: March, 373
  recurring, familial, *1966*: March, 373
Polyuria, causes of, *1968*: March, 383
  diagnosis in, *1968*: March, 386-388
Pontocaine. See *Tetracaine.*
Poquil, *1967*: Sept., 1204
Porphyria, *1966*: Sept., 1302
  diabetes and, *1965*: May, 627
  intermittent, acute, abdominal pain and, *1968*: Nov., 1277
  neuropathy and, *1968*: July, 902
  orthostatic hypotension and, *1968*: July, 812
  vs. Guillain-Barré-Strohl syndrome, *1968*: July, 901
Porta hepatis, tumors of, radiation therapy for pain of, *1968*: Jan., 205
Postextrasystolic beat, usefulness in cardiac diagnosis and prognosis, *1966*: Jan., 64-70
Posture braces, *1967*: Sept., 1333
Postphlebitic syndrome, phlebography in, *1967*: Jan., 166
Potassium, alkalosis and, *1968*: Sept., 1105
  benzothiadiazine therapy and, *1968*: Sept., 1105
  body content of, *1968*: Sept., 1103
  cardiac arrhythmias and, *1968*: Sept., 1105
  cardiovascular disease and, *1968*: Sept., **1103-1113**
  clearance after administration of spironolactone, as test for aldosteronism, *1967*: July, 864
  deficiency. See *Hypokalemia.*
  excess. See *Hyperkalemia.*
  imbalance, in renal failure, *1966*: July, 1180
  in hypertension, *1966*: Jan., 298
  loss, gastrointestinal, disorders of renal function with, *1966*: July, 999, 1000
  metabolism, disturbances, in cancer, *1966*: May, 724
    myopathy and, *1968*: March, 249
  plasma concentration, *1968*: Sept., 1104
  therapeutic administration, *1968*: Sept., 1108
Povan, *1967*: Sept., 1204
Practice, medical, contribution of social work and social agencies to, *1967*: Nov., **1485-1491**
    patient's role in, *1967*: Nov., **1507-1514**
    postgraduate education in psychiatry for, *1967*: Nov., **1363-1367**
    role of state hospital in, *1967*: Nov., **1467-1475**

Practice (*Continued*)
  supervised, for teaching psychiatry to nonpsychiatrists, *1967*: Nov., 1369
Precordium, inspection, *1966*: Sept., 1204
  palpation, *1966*: Sept., 1200
Prednisone. See also *Corticosteroids.*
  for immune suppression in renal transplantation, *1966*: July, 1167
  for rheumatoid arthritis, *1967*: Sept., 1214; *1968*: May, 693, 743
  neurologic side effects of, *1968*: July, 850
Pregnancy, endocrine functions in, *1968*: March, **253-262**
  pain relief in, *1968*: Jan., **137-146**
  prosthetic heart valves and, *1968*: Sept., 1139
  rubella in, *1967*: May, 591
  sickle cell anemia and, *1966*: Nov., 1527
  test for, in amenorrhea, *1968*: March, 349
  toxemia of, hypertension and, *1967*: July, 971; *1968*: Sept., 1234
    kidney in, *1966*: July, **1043-1053**
  varicose veins in, *1968*: Sept., 1085
Premature beats, usefulness in cardiac diagnosis and prognosis, *1966*: Jan., **51-71**
Premenstrual tension, psychologic aspects, *1967*: Nov., 1377
Pretibial myxedema in Graves' disease, *1967*: July, 917
Pripsen, *1967*: Sept., 1205
Probenecid in hyperuricemia, *1966*: July, 1036
Procaine, in office, *1968*: Jan., 175
Procaine amide, very large doses, in ventricular tachycardia, *1966*: Jan., 271
Prochlorperazine, for pain, *1968*: Jan., 51
Progestational agents in endometrial cancer, *1966*: May, 836
Progesterone test, in amenorrhea, *1968*: March, 349
Progestins, as anticancer agents, *1966*: May, 860, 866
Progestogens, oral, for amenorrhea, *1968*: March, 355
Prolactin, secretion of, excess, *1968*: March, 360
Promazine, for pain, *1968*: Jan., 51
Promethazine, for pain, *1968*: Jan., 51
Pronethalol (Alderlin), blocking action of, *1968*: Sept., 1011
Propanediols as tranquilizers, *1967*: Nov., 1455
Propanolol (Inderan), blocking action of, *1968*: Sept., 1011
  dosage, administration and side effects, *1968*: Sept., 1026-1027
  for angina pectoris, *1968*: Sept., 1031
Propanolol (Inderan) (*Continued*)
  for cardiac arrhythmias, *1967*: Sept., 1225, 1228; *1968*: Sept., 1020-1026
Propitocaine, for epidural anesthesia, *1968*: Jan., 212
Propriomazine, for pain, *1968*: Jan., 52
Prostaphlin, *1967*: Sept., 1110
Prostate, carcinoma, diagnosis, cytologic, *1966*: May, 658
    mortality, *1966*: May, 626
    radiation therapy for pain of, *1968*: Jan., 206
Protein, absorption, normal, *1968*: Nov., 1342
    studies, *1968*: Nov., 1350
  serum, test for, *1968*: Nov., 1411, 1433
Proteinuria in congestive heart failure, *1966*: Jan., 261
Proteus infections, ampicillin in, *1967*: Sept., 1138
  cephalothin in, *1967*: Sept., 1142
Protoporphyria, erythropoietic, *1966*: Sept., 1303
Provera in endometrial cancer, *1966*: May, 836
Provest, *1967*: Sept., 1263
Pruritus in liver disease, *1967*: July, 1009
Pseudoaneurysm of renal artery, arteriogram in, *1967*: Jan., 56, 58
Pseudobulbar palsy, speech disturbances in, *1968*: July, 838-841
Pseudocyesis, amenorrhea and, *1968*: March, 340
Pseudogout, synovianalysis in, *1966*: Sept., 1290
Pseudohypothyroidism, thyroid hormones in, *1966*: Sept., 1395
Pseudomonas infections, colistin in, *1967*: Sept., 1134
Pseudoxanthoma elasticum, inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Psoriasis, with arthritis, *1967*: July, 1023; *1968*: May, 506-507
Psychic. See *Mental.*
Psychiatric emergencies in adolescents, *1967*: Nov., 1445
Psychiatric problems, in aged, *1967*: Nov., **1515-1527**
  in children, *1967*: Nov., **1427-1438**, 1482
Psychiatrist and surgeon, collaboration between, *1967*: Nov., 1425
Psychiatry, and the criminal, *1967*: Nov., 1473
  courses in, basic, what a nonpsychiatric physician derives from, *1967*: Nov., **1493-1497**
    for nonpsychiatric physicians, their content and management, *1967*: Nov., 1363-1374, **1499-1506**

Psychiatry (*Continued*)
  courses in, for nonpsychiatric physicians, organization, *1967*: Nov., 1370
    teaching methods, *1967*: Nov., 1366-1369
    for pediatricians, content and methods, *1967*: Nov., 1432
  for the nonpsychiatrist, symposium on, *1967*: Nov., **1361-1527**
  for the obstetrician-gynecologist, *1967*: Nov., **1375-1380**
  in geriatrics, *1967*: Nov., **1515-1527**
  internist's role in, *1967*: Nov., **1409-1423**
  pediatric, in training of pediatricians, *1967*: Nov., **1427-1438**
  postgraduate education in, for the practicing physician, *1967*: Nov., **1363-1374, 1499-1506**
Psychologic disturbances, in aged persons, management, *1967*: Nov., **1515-1527**
  in children, *1967*: Nov., **1427-1438**
  in chronic physical illness, *1967*: Nov., **1399-1408**
  in ulcerative colitis, *1966:* March, 533
Psychologist, clinical, help for the nonpsychiatric physician by, *1967*: Nov., **1477-1483**
Psychoneurosis, internist's role, *1967*: Nov., 1417
Psychopathic behavior in adolescents, *1967*: Nov., 1449
Psychosexual problems, internist's role, *1967*: Nov., 1419
Psychosis, drug therapy, *1967*: Nov., **1453-1466**
  internist's role, *1967*: Nov., 1419
  "toxic," chronic renal failure and, *1968*: July, 846
Psychosomatic disease, *1967*: Nov., 1415
  psychologic evaluation in, *1967*: Nov., 1482
Psychotherapeutic drugs, use of, *1967*: Nov., **1453-1466**
Psychotherapy, for hypothalamic amenorrhea, *1968*: March, 341
  in gynecology, *1967*: Nov., 1379
  in mental disturbances of aged, *1967*: Nov., 1522
Pteroylglutamic acid. See *Folic acid.*
Pulmonary. See also *Lung.*
Pulmonary artery pressure, change in, with IPPB, *1967*: March, 321
Pulmonary complications of renal disease, *1966*: July, 1055-1066
Pulmonary diffusion, *1967*: March, 427-438
  capacity, measurement of, *1967*: March, 430, 432, 434, 436
Pulmonary edema, after myocardial infarction, *1968*: Sept., 1072
Pulmonary embolectomy, case for, *1967*: Jan., **185-191**
Pulmonary embolism. See *Embolism, pulmonary.*
Pulmonary fibrosis, interstitial, diffuse, *1967*: March, **439-451**
  phonocardiogram in, *1966*: Jan., 97
Pulmonary granulomatoses due to inhaled organic antigens, *1967*: March, **459-482**
Pulmonary insufficiency, congenital, phonocardiogram in, *1966*: Jan., 96
  in lung cancer, treatment, *1967*: March, 569
Pulmonary stenosis, angiocardiography in, *1966*: Jan., 132
  in adult, clinical features, *1966*: Jan., 22
  phonocardiograms in, *1966*: Jan., 99
    after amyl nitrite, *1966*: Jan., 80
Pulmonary surfactant, role, in health and disease, *1967*: March, **391-402**
Pulmonary tuberculosis. See *Tuberculosis.*
Pulsations, venous, *1966*: Sept., 1216
Pulsus paradoxus, *1966*: Sept., 1233
Pupil, Adie's, *1968*: July, 880
  Argyll Robertson, *1968*: July, 879
  Horner's, *1968*: July, 879
  neurologic diagnosis and, *1968*: July, **871-884**
  reflexes, examination, *1968*: July, 872-876
    neuroanatomic pathways, *1968*: July, 873
Pupillometer, *1968*: July, 872
Purpura due to drugs, *1967*: July, 1076, 1080
  Henoch-Schönlein, vs. juvenile rheumatoid arthritis of acute onset, *1968*: May, 575
  lung, with nephritis, *1966*: July, 1055
  thrombocytopenic. See also *Thrombocytopenia(s).*
    idiopathic, in elderly, splenectomy for, *1966*: Nov., 1534
    platelet transfusions in, *1966*: Nov., 1563, 1564
Pyelonephritis, chronic, arteriogram in, *1967*: Jan., 51
  hypertension in, *1966*: July, 1012
Pyloric obstruction, diagnosis, *1968*: Nov., 1331
  management, *1968*: Nov., **1329-1337**
    medical, *1968*: Nov., 1333-1336
    surgical, *1968*: Nov., 1336
Pyrazinamide in tuberculosis, *1966*: Sept., 1436, 1438
    drug-resistant, in children, *1967*: Sept., 1155, 1162, 1163

Pyridoxine deficiency, anemia of, *1966*: Nov., 1682
Pyrimidines, fluorinated, in metastatic gastrointestinal cancer, *1966*: March, 428, 433
Pyrvinium pamoate in pinworm infestation, *1967*: Sept., 1204, 1208
Pyuria, in urinary tract infections, *1966*: July, 1131

QUINACRINE as anticancer drug, *1966*: May, 860, 867
Quinidine, pharmacology, *1966*: Sept., 1222
  re-evaluation of, *1966*: Sept., **1221-1230**
  therapy, *1966*: Sept., 1225

RABIES, incidence and immunization, in U.S., *1967*: May, **693-700**
  vaccination, encephalitis following, *1967*: May, 707
    corticosteroids in, *1967*: Sept., 1191
Radiation, gastrointestinal effects, *1966*: May, 752
  ionizing, as cancer incitant, *1966*: May, 620, 640, 870
    in autoimmune diseases, *1966*: March, 408
  nephritis due to, *1966*: July, 969, 973, 974
  response of lymphatic channels to, *1967*: Jan., 249
  therapy, for advanced ovarian cancer, *1966*: May, 848
    for multiple myeloma, *1966*: Nov., 1575
    for pain, *1968*: Jan., **203-207**
Radio frequency current coagulation, in percutaneous cordotomy, complications, *1968*: Jan., 199
    results, *1968*: Jan., 195-198
    technique, *1968*: Jan., 189-195
Radioimmunoassay, principles, *1968*: March, 373
Radioisotope scanning. See *Scanning.*
Radium treatment, of endometrial cancer, *1966*: May, 835
RAIU. See *Iodine, radioactive, uptake test.*
Rauwolfia in hypertension, *1966*: Jan., 298; *1967*: Jan., 31, July, 985
Receptors, adrenergic. See *Adrenergic receptors.*
Rectum, anomalies, inheritance, *1968*: Nov., 1274
  carcinoma, mortality, *1966*: May, 617
Reed-Sternberg cell, *1966*: May, 821
Reflexes, disturbed, chronic renal failure and, *1968*: July, 849
  muscle stretch, cervical root pain and, *1968*: July, 775
  pupillary, examination of, *1968*: July, 872-876
    neuroanatomic pathways of, *1968*: July, 873
Refsum's disease, *1968*: July, 904
Regional colitis. See *Colitis, granulomatous.*
Regional enteritis. See *Enteritis, regional.*
Regitine. See *Phentolamine.*
Rehabilitation in chronic obstructive lung disease, *1967*: March, **349-361**
  in rheumatoid arthritis, *1968*: May, 713-714
Reiter's syndrome, vs. rheumatoid arthritis, *1968*: May, 504-505
Renal. See also *Kidney.*
Renal artery, aneurysm, *1967*: Jan., 60
  stenosis, diagnosis, *1967*: Jan., 21
  variations in caliber, at arteriography, *1967*: Jan., 49, 51
Renal hypertension. See under *Hypertension.*
Renin, formation of angiotensin and, *1968*: March, 264
  in production of hypertension, *1967*: Jan., 4
  release of, mechanism of, *1968*: March, 275
  uterine, *1968*: March, 265
Renography, isotope, *1966*: July, 941-947
Renovascular hypertension, surgical treatment, *1967*: Jan., 217, 223
Renovascular lesions in abdominal aortic aneurysm, *1966*: July, 1023
Reserpine, for hypertension, *1967*: Jan., 31, July, 986
  for poststreptococcal acute glomerulonephritis in children, *1966*: July, 1150
Resistopen, *1967*: Sept., 1110
Respiration. See also *Breathing.*
  assistance to, in hypovolemic shock, *1967*: Jan., 95
  centers, insensitivity of, *1966*: Jan., 47
  tests, as aid to cardiac auscultation, *1966*: Jan., 75
Respiratory care unit, *1967*: March, 334-337
Respiratory diseases, modern management, symposium on, *1967*: March, **267-572**
Respiratory failure, acute, pathophysiology, diagnosis, and management, *1967*: March, **323-340**
    respiratory care unit in, *1967*: March, 334-337

- Respiratory infection, acute, nondifferentiated, in children, *1967*: May, 821
  - adenoviruses and, *1967*: May, **769-779**
  - fever in, *1966*: Jan., 214
  - in adults, clinical syndromes caused by, *1967*: May, **803-818**
    - factors affecting host response, *1967*: May, 805
    - total pattern, *1967*: May, 807
    - treatment, *1967*: May, 815
  - in children, clinical syndromes, *1967*: May, **819-829**
  - lower, acute, causes and treatment, *1967*: May, 812
    - due to M. pneumoniae, location and age factors, *1967*: May, 795
  - mycoplasmas in, *1967*: May, **791-802**
  - upper, acute, causes and treatment, *1967*: May, 811
    - in children, *1967*: May, 821
- Respiratory insufficiency, surgical risk in, evaluation of, *1967*: March, **341-347**
- Respiratory syncytial virus, *1967*: May, 825
- Rest, bed, after myocardial infarction, *1968*: Sept., 1066
    - in refractory heart failure, *1968*: Sept., 1164
  - chair, in refractory heart failure, *1968*: Sept., 1164
- Reticulocyte count in evaluation of anemia, *1966*: Nov., 1696
- Reticuloendothelioses, acute renal failure in, *1967*: July, 997
- Retina, lesions of, pupillary reflexes in, *1968*: July, 877
- Retinal artery, occlusion of, fluorescein angiography of fundus in, *1968*: July, 866
- Retinopathy, chloroquine-induced, *1968*: May, 760
    - fluorescein angiography of fundus in, *1968*: July, 866
  - diabetic, absent, in long-term diabetes, *1966*: Sept., **1385-1391**
    - fluorescein angiography of fundus in, *1968*: July, 858
- Retroperitoneal band, arteriogram in, *1967*: Jan., 58, 59
- Retroperitoneal fibrosis, *1966*: July, **1091-1099**
- RF. See *Rheumatoid factor.*
- Rheumatic diseases. See also *Rheumatism, Arthritis* and *Arthropathy.*
- Rheumatic fever, chemoprevention, *1966*: Jan., **279-285**
  - synovianalysis in, *1966*: Sept., 1288, 1289
- Rheumatic heart disease. See *Heart disease, rheumatic.*
- Rheumatism, palindromic, vs. rheumatoid arthritis, *1968*: May, 509-510
- Rheumatoid arthritis. See *Arthritis, rheumatoid.*
- Rheumatoid factor, epidemiology of rheumatoid arthritis and, *1968*: May, 487-488
  - in rheumatoid arthritis, significance of, *1968*: May, **533-538**
    - tests for, 1966: Sept., 1284; *1968*: May, 545
- Rhinovirus infections in children, *1967*: May, 827
- Rhinoviruses, common cold and, *1967*: May, 765
- Riboflavin deficiency, oral lesions, *1966*: March, 366
- Riley-Day syndrome, *1968*: July, 900
- Ritalin. See *Methylphenidate.*
- Roentgen diagnosis, of atrial septal defects, *1967*: July, 953
  - of heart disease, techniques, *1966*: Jan., **127-139**
  - of renal disease, *1966*: July, **957-967**
- Roentgen examination, in bleeding esophageal varices, *1968*: Nov., 1463
  - in colitis, *1968*: Nov., 1390
  - in liver disease, *1968*: Nov., 1408
  - in rheumatoid arthritis, *1968*: May, **655-665**
    - juvenile, *1968*: May, 577, 580
  - of skull, cerebellopontine angle lesions and, *1968*: July, 790
    - chromophobe adenoma and, *1968*: July, 829
- Roentgen immunosuppression in renal transplantation, *1966*: July, 1166
- Roentgen study of renal function with isotopes, *1966*: July, 941-947
- Roentgen treatment, of cancer, preoperative, argument for, *1967:* Jan., 255
    - response of lymphatic channels to, *1967*: Jan., 249
  - of chronic granulocytic leukemia, *1966*: May, 805
  - of Hodgkin's disease, *1966*: May, 824, Nov., 1598
    - palliative, *1966*: Nov., 1605
  - of inoperable lung cancer, *1967*: March, 564
- Roentgenologic procedures, effect on renal function, *1966*: July, **969-977**
- Rolitetracycline, toxic reactions, *1967*: July, 937
- Rondomycin, *1967*: Sept., 1128
- Rotor syndrome, *1968*: Nov., 1422
- Rubella, in pregnancy, *1967*: May, 591
  - intrauterine (congenital), *1967*: May, 589

Rubella (*Continued*)
  neurologic complications, *1967*: May, 711
  problems and progress, *1967*: May, **587-598**
  syndrome, *1967*: May, 589
  virologic aspects and prospects for vaccine, *1967*: May, 592
Rubella synovitis, vs. juvenile rheumatoid arthritis of polyarticular onset, *1968*: May, 578
Rubeola. See *Measles.*

SACROILIAC belts, *1967*: Sept., 1336
Sacroiliac joints, in ankylosing spondylitis, *1968*: May, 518
  in rheumatoid arthritis, *1968*: May, 518
Salicylates, for rheumatism, *1967*: Sept., 1213
  for rheumatoid arthritis, *1968*: May, 699, **703-706**
Saline load test, in pyloric obstruction, *1968*: Nov., 1332
Salmonella infections, *1967*: May, 647
  ampicillin in, *1967*: Sept., 1138
  epidemiology and clinical features, *1967*: July, **1015-1018**
Salt, absorption, normal, *1968*: Nov., 1343
Sarcoidosis, clinical features and management, *1967*: March, **483-502**
  corticosteroid therapy, *1967*: March, 497
  extrathoracic, *1967*: March, 496
  intrathoracic, *1967*: March, 489, 492
Sarcolysins in multiple myeloma, *1966*: Nov., 1570
Sarcomas, electron microscopy in, *1966*: May, 893
Scalenus anticus syndrome, *1968*: July, 777
Scanner, moving, *1966*: May, 690
  stationary, *1966*: May, 694
Scanning, bone, for metastatic cancer, *1966*: May, **701-710**
  boutrophedonic, *1966*: July, 953
  in cancer diagnosis, *1966*: May, **689-700**
  instantaneous two-dimensional (fluoroscopic), *1966*: July, 953
  liver, *1968*: Nov., 1412
    in cancer diagnosis, *1966*: May, 695, 756
  lung, in pulmonary embolism, *1967*: Jan., 177, 180
  pancreatic, in cancer diagnosis, *1966*: May, 758
  renal, in evaluation of function, *1966*: July, 947-954
Schistosomiasis mansoni, ectopic central nervous system lesions of, *1966*: March, **597-602**
School, difficulties, in adolescents, *1967*: Nov., 1441
Sciatica, enigma of, *1968*: Jan., **183-188**
  experimental findings in causes of, *1968*: Jan., 184
  inflammation and, *1968*: Jan., 186
Scintiscanning, in classification of thyroid nodules, *1968*: March, 412
Scleroderma, cutaneous melanosis in, *1966*: March, 351
  gastrointestinal manifestations, *1966*: March, 417
  lung involvement in, *1966*: July, 1062
  renal complications, *1966*: July, 1062
  vs. rheumatoid arthritis, *1968*: May, 560, 562
Sclerosis, amyotrophic lateral, speech disturbances in, *1968*: July, 838-842
  systemic, progressive. See *Scleroderma.*
Scoliosis, braces, *1967*: Sept., 1327
  incipient and early, diagnosis, *1967*: Sept., 1329
Secretin, structure, secretion, and action, *1968*: Nov., 1300
Secretin-pancreozymin test, in chronic pancreatitis, *1968*: Nov., 1488
Secretions, management, by aerosol therapy, *1967*: March, 307
    in respiratory failure, *1967*: March, 332
Sedatives, for pain, *1968*: Jan., **47-53**
Seizures, absence, features of, *1968*: July, 961
    medical treatment for, *1968*: July, 963
  chronic renal failure and, *1968*: July, 846-847
  convulsive, classification of, *1968*: July, 960
    medical treatment for, *1968*: July, **959-975**. See also *Anticonvulsants.*
  electroencephalographic evaluation of, *1968*: July, 938, **949-957**
    activation of abnormalities, *1968*: July, 952-953
    localization of origin, *1968*: July, 953-957
  focal at onset, medical treatment for, *1968*: July, 966
  indications for surgery for, *1968*: July, 973
  mixed, medical treatment for, *1968*: July, 966
  nonconvulsive, features of, *1968*: July, 961
    medical treatment for, *1968*: July, 963
  recurrent, diazepam for, *1968*: July, **977-987**

Seizures (*Continued*)
  tonic-clonic, isolated, medical treatment for, *1968*: July, 968
  vs. orthostatic hypotension, *1968*: July, 811
  withdrawal, medical treatment for, *1968*: July, 969
Selenium sulfide, topical, in fungus infections, *1967*: Sept., 1184
Sella turcica, changes in, chromophobe adenoma and, *1968*: July, 829
Semopen, *1967*: Sept., 1108
Sengstaken-Blakemore tube, in therapy of bleeding esophageal varices, *1968*: Nov., 1466
Sensitivity. See also *Hypersensitivity.*
  factors, in emphysema, *1967*: March, 278
    in pulmonary granulomatoses, *1967*: March, 459
  microbial, tests for, *1966*: Sept., 1430
Septal defect, aortic, *1967*: Jan., 196
  atrial, angiocardiography in, *1966*: Jan., 131
    in adults, clinical features, *1966*: Jan., 19
    manifestations, *1967*: July, **949-957**
  ventricular, in adult, clinical picture, *1966*: Jan., 24
    phonocardiogram in, *1966*: Jan., 102
      after amyl nitrite, *1966*: Jan., 81
    uncomplicated, second heart sound in, *1966*: Jan., **111-114**
Sequoiosis, *1967*: March, 459, 460
Serotonin, rheumatoid arthritis inflammation and, *1968*: May, 625
Serum, in rheumatoid arthritis, abnormalities, *1968*: May, 543-544, **559-565**
    tests, *1968*: May, 544-547
Serum hepatitis vs. infectious hepatitis, *1967*: May, 658
Serum sickness, vs. juvenile rheumatoid arthritis of polyarticular onset, *1968*: May, 578
Serum sickness-like reactions to drugs, *1967*: July, 1076, 1084
Sex chromatin abnormalities in cancer, *1966*: May, 882
Sex glands. See *Ovaries* and *Testes.*
Sheehan's syndrome, *1968*: March, 342
Shigellosis, age and nutritional factors, *1967*: May, 649
  epidemiology and clinical features, *1967*: July, **1015-1018**
Shock, adrenergic receptor blockers and, *1968*: Sept., **1049-1060**
  cardiogenic, after myocardial infarction, *1968*: Sept., 1073
  effects on blood pressure, *1967*: July, 977
Shock (*Continued*)
  hemodynamic defect in, *1968*: Sept., 1050-1051
  hypovolemic, diagnosis, *1967*: Jan., 87
    pathophysiology, *1967*: Jan., 84
    treatment, changing concepts, *1967*: Jan., **83-96**
  in myocardial infarction, treatment, physiologic basis, *1967*: Jan., **69-81**
  low molecular weight dextran in, *1967*: Sept., 1292
  serum enzymes in, *1966*: Jan., 183
  sympathoadrenal response to, *1968*: Sept., 1051-1056
  sympathomimetic drugs in, *1967*: July, 984
  venous tone in, *1968*: Sept., 1082
Shoulder, in rheumatoid arthritis, *1968*: May, 497
    surgery of, *1968*: May, 724
Shoulder-hand syndrome, *1968*: Jan., 119
Sickle cell anemia, clinical manifestations and treatment, *1966*: Nov., **1519-1532**
Sigmoidoscopy, in colitis, *1968*: Nov., 1389
Sitosterol (Cytellin), for hypercholesterolemia, *1968*: Sept., 1253
Sjögren's syndrome, gastrointestinal manifestations, *1966*: March, 402
Skeletal system. See *Bone(s).*
Skin, grafts, ischemic, hyperbaric oxygen for, *1967*: Sept., 1311
  lesions, in adrenocortical disease, *1967*: July, 886
    in Graves' disease, *1967*: July, 917
    in rheumatoid arthritis, *1967*: July, 1023
    in ulcerative colitis, *1966*: March, 532; *1967*: July, 1012
  pigmentation, gastrointestinal disorders with, *1966*: March, **347-602**
  reactions, to drugs, *1967*: July, **1073-1088**
Skull, roentgen examination, cerebellopontine angle lesions and, *1968*: July, 790
SLE. See *Lupus erythematosus, systemic.*
Sleepiness, excessive and recurrent, *1968*: July, 781
Smallpox, neurologic complications, *1967*: May, 711
  vaccination, encephalitis following, *1967*: May, 704
      corticosteroids in, *1967*: Sept., 1192
    for foreign travel, *1967*: May, 844
    in infants and children, *1967*: May, 584
Smoking, and cancer, *1966*: May, 638, 644, 645
  stroke incidence and, *1967*: Jan., 109
  thrombosis and, *1967*: Jan., 158

Sodium, excretion, tissue hormones and, *1968*: March, 276-278
  imbalance, in renal failure, *1966*: July, 1179
  loss, gastrointestinal, disorders of renal function with, *1966*: July, 999, 1000
    in cancer, *1966*: May, 722
  metabolism, disturbances in cancer, *1966*: May, 719
  restriction, for hypertension, *1968*: Sept., 1231
    in refractory heart failure, *1968*: Sept., 1165
Sodium bicarbonate in hypovolemic shock, *1967*: Jan., 95
Sodium dextrothyroxine, clinical uses, *1966*: Sept., 1393
Sodium levothyroxine, clinical uses, *1966*: Sept., 1393
Sodium levotriiodothyronine, clinical uses, *1966*: Sept., 1393
Sodium salicylate, site of action of, *1968*: Jan., 8
Solganol. See *Gold thioglucose.*
Somatotropin, influence on renal function, *1966*: July, 985
  radioimmunoassay of, *1968*: March, 373
  secretion of, decreased, *1968*: March, 367
    excess, *1968*: March, 361
      diagnosis of, *1968*: March, **371-380**
Sore throat, causes and treatment, *1967*: May, 810
  in rheumatoid arthritis, *1967*: July, 1020
Sounds, cardiac. See under *Heart.*
Spansules, iron, in anemia, *1966*: Nov., 1716
Sparine. See *Promazine.*
Spasticity, pain related to, neurolytic substances for, *1968*: Jan., 165
Speech, disturbed, clinical observation of, *1968*: July, 835-837
  kinds of, *1968*: July, 837-841
  neurologic disease and, *1968*: July, **835-844**
Spherocytosis, hereditary, in elderly, splenectomy for, *1966*: Nov., 1536
Spinal cord, hypertrophy of, cervical root pain and, *1968*: July, 775
  pain in, *1968*: Jan., 115
  pain transmission in, *1968*: Jan., 16
Spinal fluid. See *Cerebrospinal fluid.*
Spine, cervical, involvement, in rheumatoid arthritis, *1967*: July, 1021
  in rheumatoid arthritis, *1968*: May, 501
  injury or disease, back braces in, *1967*: Sept., **1315-1343**
  nerve blocks in, *1968*: Jan., 125
Spironolactone (Aldactone), for hypertension, *1968*: Sept., 1231
  for primary aldosteronism, *1968*: Sept., 1228
  for refractory heart failure, *1968*: Sept., 1174
Spironolactone test for aldosterone secretion, *1967*: July, 864
Spleen, in rheumatoid arthritis, *1967*: July, 1022
  infections, anemia in, *1966*: Nov., 1710
Splenectomy, in aged persons, *1966*: Nov., **1533-1558**
  in "spent" polycythemia, *1966*: Nov., 1515
Splenomegaly, in elderly, splenectomy for, *1966*: Nov., **1533-1558**
  with rheumatoid arthritis, *1968*: May, 529
    juvenile, *1968*: May, 570
Splints and appliances, for rheumatoid arthritis, *1968*: May, 712-713
Spondylitis, ankylosing, epidemiology of, *1968*: May, 524
    familial factors in, *1968*: May, 524
    low back pain and, *1968*: Jan., 64
    prognosis in, *1968*: May, 525-526
    radiation therapy for pain of, *1968*: Jan., 203
    sex and, *1968*: May, 524
    systemic manifestations, *1968*: May, 523-524
    vs. rheumatoid arthritis, *1968*: May, 503-504, 512, **517-526**
    with regional enteritis or ulcerative colitis, *1968*: May, 508, 512
  Marie-Strümpell. See *Spondylitis, ankylosing.*
  rheumatoid. See *Spondylitis, ankylosing.*
  tuberculous, low back pain and, *1968*: Jan., 63
Spondylolisthesis, low back pain and, *1968*: Jan., 59
Sporotrichosis, pulmonary, *1967*: March, **519-527**
Sprue, *1968*: Nov., 1360
  cutaneous melanosis with, *1966*: March, 351
  nontropical, lymphomas and, *1966*: May, 749
  tropical, *1968*: Nov., **1367-1385**
    treatment, *1968*: Nov., 1379
Sputum cultures in management of infections, *1966*: Sept., 1423
Stains, for cytologic diagnosis, *1966*: May, 663
Staphcillin, *1967*: Sept., 1109

Staphylococcal infections, postoperative, in cancer patients, treatment, *1966*: May, 795
  treatment, *1967*: March, 543, Sept., 1116, 1118
Status asthmaticus, management, current concepts, *1967*: March, **373-389**
Status epilepticus, diazepam for, *1968*: July, **977-987**
  medical treatment for, *1968*: July, 967
Steatorrhea, chronic pancreatitis and, *1968*: Nov., 1488
  in pancreatic disease, *1966*: March, 454
Stein-Leventhal syndrome, *1968*: March, 345
Stelazine, *1967*: Sept., 1255
Stenosis. See name of organ.
Sternoclavicular joint, in rheumatoid arthritis, *1968*: May, 497
Steroid(s), synthesis, by human ovary, *1967*: July, **903-913**
  therapy. See *Corticosteroids*.
    in cancer, *1966*: May, 859, 864
    neurologic side effects of, *1968*: July, 850
Steroidogenesis, pathways of, *1967*: July, 903
Stevens-Johnson disease, drug-induced, *1967*: July, 1076, 1078
"Stiff heart" syndrome, as cause of heart failure, *967*: July, **959-966**
Stilbamidine, for trigeminal neuralgia, *1968*: July, 797
Stilbazium iodide in pinworm infestation, *1967*: Sept., 1207, 1208
Stomach, carcinoma, diagnosis, cytologic, *1966*: May, 659
      newer techniques, *1966*: May, 754
    environmental factors in, *1968*: Nov., 1279
    genetic factors, *1968*: Nov., 1279
    mortality, *1966*: May, 616, 640, 641, 642
  cytological examination of, *1968*: Nov., 1320
  diseases, autoimmune, *1966*: March, 403
    malnutrition caused by, *1968*: Nov., 1400
    pain patterns in, *1968*: Jan., 107
  hypersecretion, in Zollinger-Ellison syndrome, *1966*: March, 476
  ulcer. See *Peptic ulcer*.
Stomatitis, aphthous, *1966*: March, 365
  herpetic, *1966*: March, 364
Stone(s). See *Calculus(i)*.
Stool cultures in management of infections, *1966*: Sept., 1429
Streptococcal infections, acute glomerulonephritis following, in children, *1966*: July, **1141-1158**
  respiratory, in adults, *1967*: May, 812
Streptomycin, for bacterial endocarditis, *1968*: Sept., 1098
  in tuberculosis, *1966*: Sept., 1436, 1437
    of kidney, *1966*: July, 1138
  toxicity, *1967*: July, 936
Stress, fibrinolysis due to, *1967*: July, 1063
  psychological, as coronary risk factor, *1966*: Jan., 241
    gastrointestinal response, *1966*: March, **591-595**
  role, in thrombosis, *1967*: Jan., 154
  ulcers, etiology, diagnosis and treatment, *1966*: Sept., **1447-1455**
Stroke, hemorrhagic, *1968*: Sept., **1193-1212**
    causes of, *1968*: Sept., 1200-1204
    cerebrospinal fluid in, *1968*: Sept., 1198
    hypertension and, *1968*: Sept., 1204-1206
    preventive measures, *1968*: Sept., 1209
    treatment for, *1968*: Sept., 1207-1209
    vs. occlusive, *1968*: Sept., 1193
  prevalence of, *1967*: Jan., 105
  preventability of, *1967*: Jan., **105-111**
  prevention, anticoagulants in, *1967*: Jan., 110
    surgery in, *1967*: Jan., 110, **113-122**
  risk factors, *1967*: Jan., 107
Strontium-85 scanning, in bone metastases, *1966*: May, 702
Subaortic stenosis, congenital, surgical indications and treatment, *1966*: Jan., 314
  in adult, clinical picture, *1966*: Jan., 25
  phonocardiogram in, *1966*: Jan., 105
    after isoproterenol, *1966*: Jan., 85
Subluxation of joints, in rheumatoid arthritis, *1968*: May, 660
Subclavian artery and vein, compression of, *1968*: July, 777
Succinimides, for seizures, *1968*: July, 963
Sucrase-isomaltase deficiency, *1968*: Nov., 1360
Suction, nasogastric, for pyloric obstruction, *1968*: Nov., 1333
Sulfadimethoxine in chronic bronchitis, *1967*: Sept., 1177
Sulfinpyrazone in hyperuricemia, *1966*: July, 1037
Sulfonamides, for pulmonary mycoses, *1967*: March, 524
  meningococcal disease resistant to, *1967*: May, **719-727**

Sulfonamides (*Continued*)
  photosensitivity due to, *1966*: Sept., 1300
  toxic reactions, *1967*: July, 936
Sulfonylureas, photosensitivity due to, *1966*: Sept., 1299
Sulthiame (Ospolot), for seizures, *1968*: July, 972
Summation gallop, *1966*: Jan., 101
Sunlight, diseases caused or aggravated by, *1966*: Sept., **1295-1311**
Sun-protective creams, *1966*: Sept., 1309
Suppuration. See *Abscess.*
Supra-aortic stenosis, surgical indications and treatment, *1966*: Jan., 322
Sural nerve, biopsy of, *1968*: July, 886-889
Surfactant, pulmonary, role, in health and disease, *1967*: March, **391-402**
Surgery, for cardiac complications of myocardial infarction, *1968*: Sept., **1115-1131**
  for Hodgkin's disease, *1966*: Nov., 1607
  for pain relief, pain transmission and, *1968*: Jan., 19-20
  general practice of, problems with pain in, *1968*: Jan., **103-109**
  orthopedic, for rheumatoid arthritis, *1968*: May, **717-731**
  renal function during and after, *1966*: July, **979-983**
Surgical risk in respiratory handicaps, *1967*: March, **341-347**
Sympathectomy, for relief of pain, *1968*: Jan., **147-159**
    lumbar, *1968*: Jan., 158
    thoracic, *1968*: Jan., 156
Sympathomimetic drugs, *1967*: July, 978, 982
Symptom removal, dangers, in adolescence, *1967*: Nov., 1446
Syncillin, *1967*: Sept., 1108
Syncope, vasovagal, vs. orthostatic hypotension, *1968*: July, 811
Synovial fluid, aspiration, *1966*: Sept., 1282
  evaluation, in joint disease, *1966*: Sept., **1281-1293**
    in rheumatoid arthritis, *1968*: May, 539-543
Synovianalysis, *1966*: **1281-1293**
Synovitis, acute, in rheumatoid arthritis, *1968*: May, 608
  rubella, vs. juvenile rheumatoid arthritis of polyarticular onset, *1968*: May, 578
Syphilis, anemia of, *1966*: Nov., 1709
  biologic aspects, *1967*: May, 736
  chronic biologic false-positive test, in connective tissue disease, *1966*: Sept., **1271-1279**
Syphilis (*Continued*)
  control, homosexual and, *1967*: May, 747
    teenager and, *1967*: May, 746
  epidemiology and prevention, *1967*: May, **735-751**
  recrudescence of, *1967*: May, 740
Syringomyelia, lumbosacral, *1968*: July, 899
Systemic diseases, arthropathies in, *1966*: March, **417-425**
  cutaneous manifestations, *1966*: March, **349-359**
  gastrointestinal tract and, symposium on, *1966*: March, **347-602**
  oral manifestations, *1966*: March, 361-369
  pancreas and, *1966*: March, **449-460**

T_3 TEST, *1968*: March, 468
Tachycardia, atrial, paroxysmal, propanolol for, *1968*: Sept., 1020
  electrical conversion in, *1965*: Sept., 1343, 1344
  supraventricular, after myocardial infarction, *1968*: Sept., 1067
    paroxysmal, propanolol for, *1968*: Sept., 1020
  ventricular, procaine amide for, *1966*: Jan., 271
    propanolol for, *1968*: Sept., 1025
Tamponade, cardiac, uremic pericarditis and, *1968*: Sept., 1237-1241
Teenager, in syphilis control, *1967*: May, 746
Teeth, in hyperparathyroidism, *1967*: July, 876
Tego-Pen, *1967*: Sept., 1112
Tegretol. See *Carbamazepine.*
Telangiectasia, hemorrhagic, inheritance, and gastrointestinal manifestations, *1968*: Nov., 1277
Tension, as coronary risk factor, *1966*: Jan., 241
Test(s), alkaline phosphatase, *1968*: Nov., 1410
  angiotensin infusion, for hypertension, *1967*: July, 867
  bile pigment excretion, *1968*: Nov., 1412
  bilirubin, *1968*: Nov., 1409
  blood ammonia, *1968*: Nov., 1412
  bromsulphalein excretion, *1968*: Nov., 1411
  cholesterol levels, *1968*: Nov., 1432
  chronic biologic false-positive, for syphilis, in connective tissue disease, *1966*: Sept., **1271-1279**

Test(s) (*Continued*)
  compatibility, appraisal of, *1966*: Nov., **1643-1652**
  Coombs antiglobulin, in diagnosis of anemias, *1966*: Nov., 1699
  dexamethasone, for Cushing's syndrome, *1967*: July, 892, 899
  for anemias, *1966*: Nov., **1689-1702**
  for antinuclear factors in rheumatoid arthritis, *1968*: May, **559-565**
  for fibrinolysis, *1967*: July, 1066
  functional, as aid to cardiac auscultation, *1966*: Jan., **73-89**
    of lung. See under *Lung.*
  histamine, of gastric secretion, *1968*: Nov., 1307
  in adolescent problems, *1967*: Nov., 1442
  in ankylosing spondylitis, *1968*: May, 523-524
  in jaundice, *1968*: Nov., 1427-1437
  in liver disease, *1968*: Nov., **1407-1416**
  in malabsorption, *1968*: Nov., 1350
  in orthostatic hypotension, *1968*: July, 814
  in pancreatic disease, *1968*: Nov., **1483-1492**
  in rheumatoid arthritis, *1968*: May, **539-548**
    juvenile, *1968*: May, 574, 577
  inhalation, provocative, in farmer's lung, *1967*: March, 481
  insulin, of gastric secretion, *1968*: Nov., 1309
  lactic dehydrogenase, *1968*: Nov., 1410
  Lundh, in chronic pancreatitis, *1968*: Nov., 1491
  pentagastrin, of gastric secretion, *1968*: Nov., 1308
  saline load, in pyloric obstruction, *1968*: Nov., 1332
  secretin-pancreozymin, in chronic pancreatitis, *1968*: Nov., 1488
  sensitivity, microbial, *1966*: Sept., 1430
  serologic, *1966*: Sept., 1430
    for farmer's lung, *1967*: March, 480
  serum proteins, *1968*: Nov., 1411
  spironolactone, for aldosteronism, *1967*: July, 864
  thymol turbidity, *1968*: Nov., 1411
  transaminases, *1968*: Nov., 1410
Testes, chromophobe adenoma and, *1968*: July, 830
Testosterone, erythropoiesis and, *1968*: March, 232
  leukopoiesis and, *1968*: March, 239
Tetany in hyperparathyroidism, *1967*: July, 880
Tetracaine, for epidural anesthesia, *1968*: Jan., 212
  in office, *1968*: Jan., 175, 178
Tetrachlorsalicylamide, photodermatitis due to, *1966*: Sept., 1301
Tetracycline, for bacterial endocarditis, *1968*: Sept., 1098
  fluorescence test, for gastric cancer, *1966*: May, 755
  photosensitivity due to, *1966*: Sept., 1299
  toxicity, *1965*: May, 715, Sept., 1397; *1967*: July, 937
Tetralogy of Fallot, in adult, clinical picture, *1966*: Jan., 29
  phonocardiogram in, *1966*: Jan., 101
    after amyl nitrite, *1966*: Jan., 82
Thalamus, pain originating in, *1968*: Jan., 116
Thalassemias, *1966*: Nov., 1682
THAM in hypovolemic shock, *1967*: Jan., 95
Theophylline in chronic bronchitis, *1967*: Sept., 1178
Thiabendazole in pinworm infestation, *1967*: Sept., 1206, 1208
Thiamine deficiency, heart failure due to, *1966*: Jan., 303
Thiazide diuretics, for hypertension, *1968*: Sept., 1231
  for refractory heart failure, *1968*: Sept., 1169
Thiazides in hypertension, *1966*: Jan., 297; *1967*: Jan., 30
Thio-TEPA, as anticancer agent, *1966*: May, 858, 862
  in breast cancer as adjunct to surgery, *1966*: Sept., 1459
  in Hodgkin's disease, *1966*: May, 827, Nov., 1606
Thoracic outlet syndromes, *1968*: July, 777-778
Thorazine. See *Chlorpromazine.*
Thresher's lung, *1967*: March, 460
Throat, sore, causes and treatment, *1967*: May, 810
  in rheumatoid arthritis, *1967*: July, 1020
Thrombin, *1966*: Sept., 1261
Thrombocytopenia, amegakaryocytic (autoimmune), platelet transfusions in, *1966*: Nov., 1563
  megakaryocytic (immune) platelet transfusions in, *1966*: Nov., 1564
  oral lesions, *1966*: March, 368
  self-limiting, acute, platelet transfusions in, *1966*: Nov., 1563
Thrombocytopenic purpura, idiopathic, in elderly, splenectomy for, *1966*: Nov., 1534
Thromboembolism, atrial fibrillation in, conversion of, *1966*: Jan., 117
  little publicized aspects, *1967*: Jan., **151-159**
  renal, in heart disease, *1966*: Jan., 262

Thrombokinase, *1966*: Sept., 1261
Thrombophlebitis, in carcinoma of lung, *1967*: July, 1043
  phlebography in, *1967*: Jan., 163
Thrombosis, biomechanics of, *1966*: Sept., 1267
  complicating aminocaproic acid therapy, *1966*: Nov., 1675
  electron microscopic studies, *1967*: Jan., 147
  gout and, *1967*: Jan., 158
  heparin in, effects, *1967*: Jan., 151
  of renal endarterectomy site, arteriogram in, *1967*: Jan., 55
  smoking and, *1967*: Jan., 127
  stress in, role, *1967*: Jan., 154
  venous, fever in, *1966*: Jan., 216
Thrombus, formation of, at prosthetic heart valve, *1968*: Sept., 1134
Thymol turbidity test, *1968*: Nov., 1411, 1435
Thyroglobulin, clinical uses, *1966*: Sept., 1393
Thyroid, desiccated, clinical uses, *1966*: Sept., **1393-1402**
Thyroid acropachy, *1968*: March, **393-398**
Thyroid gland, carcinoma, radiation therapy for pain of, *1968*: Jan., 206
    thyroid hormones in, *1966*: Sept., 1399
  chromophobe adenoma and, *1968*: July, 831
  disease, occult, *1966*: March, **575-580**
  disorders, amenorrhea and, *1968*: March, 343
    clubbing of fingers and toes in, *1968*: March, **393-398**
    periosteal bone formation in, *1968*: March, **393-398**
  function, erythropoiesis and, *1968*: March, 234
    in amenorrhea, *1968*: March, 350
    leukopoiesis and, *1968*: March, 239
    pregnancy and, *1968*: March, 257-259
    tests of, 1967: July, 923; *1968*: March, **463-472**
      thyroid hormone, *1966*: Sept., 1400
  gastroenterology and, *1966*: March, **581-590**
  hormones, diagnostic uses, *1966*: Sept., 1399
    influence on renal function, *1966*: July, 993
    therapeutic use, *1966*: Sept., **1393-1402**
Thyroid suppression therapy, for goiter, *1968*: March, 413
Thyroiditis, Hashimoto's, chronic BFP test for syphilis in, *1966*: Sept., 1274, 1277
Thyroiditis (*Continued*)
  Hashimoto's, parietal cell antibody and, *1968*: Nov., 1286
Thyroid-stimulating hormone, production, in nonthyroid cancer, *1966*: May, 775
Thyrotoxic crisis, *1967*: July, 922
Thyrotoxicosis. See also *Hyperthyroidism.*
  muscle wasting and, *1968*: March, 243
  parietal cell antibody and, *1968*: Nov., 1286
  radioactive iodine therapy for, *1968*: March, **417-429**
Thyroxine, clinical uses, *1966*: Sept., **1393-1402**
Tibial nerve, anterior, biopsy of, *1968*: July, 886
Tic douloureux, *1968*: Jan., 111
  medical treatment of, *1968*: July, **797-800**
Tinel's sign, *1968*: July, 778
Tissue hormones, *1968*: March, **263-281**
Toes, clubbing of, hyperthyroidism and, *1968*: March, **393-398**
Tofranil, *1967*: Sept., 1253
Tolbutamide in diabetes, *1966*: Sept., 1376, 1378
Tolbutamide tolerance test, in hypoglycemia, *1968*: March, 286-293
Tolerance, to drugs, *1968*: Jan., 33
Tolnaftate, topical, in fungus infections, *1967*: Sept., 1182
Tolseram. See *Mephenesin.*
Tolserol. See *Mephenesin.*
Tomography in renal disease, *1966*: July, **957-967**
Tongue, normal and pathologic anatomy, *1966*: March, 362
Tonsillitis, acute, causes and treatment, *1967*: May, 810
Tophi of gout, *1967*: July, 1036, 1038
Toxemia, of pregnancy, hypertension and, *1967*: July, 971; *1968*: Sept., 1234
Tranquilizers, for pain, *1968*: Jan., **47-53**
  major, *1967*: Nov., 1456
  minor, *1967*: Nov., 1455
  uses of, *1968*: Jan., 50
Transaminases, serum, in pulmonary embolism, *1967*: Jan., 176
    tests for, *1968*: Nov., 1410, 1428, 1430, 1431
Transfusions, compatibility tests, appraisal, *1966*: Nov., **1643-1652**
  in anemia, indications, contraindications and risks, *1966*: Nov., 1717
  in bleeding esophageal varices, *1968*: Nov., 1459
  in coagulation defects, *1967*: Sept., 1242
  in hypovolemic shock, *1967*: Jan., 91
  platelet, use of, *1966*: Nov., **1559-1568**
Transplantation, of kidney, present status, *1966*: July, **1165-1173**

Transplantations (*Continued*)
  of tissues and organs, hyperbaric oxygen in, *1967*: Sept., 1312
  pneumonia, *1966*: July, 1057
Transposition of great vessels, corrected, clinical picture, *1966*: Jan., 30
  pathology, *1966*: Jan., 8
Trauma, arthritis from, *1968*: May, 580
  to back, *1968*: Jan., 60
Triamcinolone, for rheumatoid arthritis, *1968*: May, 743
Triamterene (Dyrenium), for hypertension, *1968*: Sept., 1231
  for refractory heart failure, *1968*: Sept., 1174
Trichloroethylene, for postoperative pain, *1968*: Jan., 88
  for trigeminal neuralgia, *1968*: July, 797
  in labor, *1968*: Jan., 142
Tricuspid valve, atresia and stenosis, pathologic complexes, *1966*: Jan., 11
  lesions, bedside diagnosis, *1966*: Sept., 1217
Triethylene thiophosphoramide. See *Thio-TEPA*.
Trifluoperazine in alcoholism, *1967*: Sept., 1255
Trigeminal nerve, cerebellopontine angle lesions and, *1968*: July, 789
Trigeminal neuralgia, medical treatment of, *1968*: July, **797-800**
Triglycerides, medium chain, for tropical sprue, *1968*: Nov., 1380
Triiodothyronine, clinical uses, *1966*: Sept., **1393-1402**
Trilene. See *Trichloroethylene*.
TRIS buffer in hypovolemic shock, *1967*: Jan., 95
Tropical sprue. See *Sprue, tropical*.
Trypsin as aerosol, *1967*: March, 312
Tuberculin tests, in infants and children, *1967*: May, 582, 583, 584
Tuberculosis, BCG vaccination and, *1967*: May, **753-764**
  chemoprophylaxis, *1966*: Sept., 1444
  extrapulmonary, *1966*: Sept., 1442
  hematologic disorders due to, *1966*: Nov., 1706
  in children, drug-resistant, newer and second-line drugs in, *1967*: Sept., **1153-1167**
  leukoerythroblastosis in, *1966*: May, 782
  miliary, *1966*: Sept., 1443
  of adrenal glands, *1968*: March, 327
  of kidney, arteriography in, *1967*: Jan., 65
    diagnosis and treatment, *1966*: July, **1137-1139**

Tuberculosis (*Continued*)
  surgery in, *1966*: Sept., 1440
  treatment, *1966*: Sept., **1433-1445**
Tubules, convoluted, of kidney, *1966*: July, 932, 933
Tumors, due to drugs, *1967*: July, 1084
  inoperable, hyperbaric oxygen in, *1967*: Sept., 1309
  of organs. See under names of organs.
Turcot's syndrome, *1966*: March, 384
Typhoid fever, age incidence, *1967*: May, 647
  ampicillin in, *1967*: Sept., 1138
  vaccine, *1967*: May, **617-623**
Tyrosinosis, inheritance and gastrointestinal manifestations, *1968*: Nov., 1278

ULCER, duodenal. See *Peptic ulcer*.
  jejunal, after Billroth II reconstruction, gastrin and, *1968*: Nov., 1299
  of foot, perforating, *1968*: July, 899
  peptic. See *Peptic ulcer*.
Ulcerative colitis. See *Colitis, ulcerative*.
Ultraviolet sources, percentage composition, *1966*: Sept., 1297
Undernutrition, cardiovascular disease and, *1966*: Jan., 302
  oral lesions, *1966*: March, 366
Unipen, *1967*: Sept., 1111
Uremia, gastrointestinal manifestations, *1966*: March, 508
  in acute renal failure, *1967*: July, 998
  in chronic renal failure, *1966*: July, 1176, 1182, 1183
    complications, *1966*: July, 1183
    relief of symptoms, *1966*: July, 1184
  neuropathy and, *1968*: July, 906
Uremic acidosis, *1966*: July, 1182
Uremic pneumonitis, *1966*: July, 1064
Uremic syndrome, hemolytic, renal failure in, *1967*: July, 998
Ureters, obstruction, by abdominal aortic aneurysm, *1966*: July, 1025
    intrarenal arteriogram in, *1967*: Jan., 61, 62
Urethane, as anticancer drug, *1966*: May, 860, 867
  in multiple myeloma, *1966*: Nov., 1574
Urethra, topical analgesia of, *1968*: Jan., 179
Urethritis, with arthritis, *1968*: May, 504
Uric acid, excess, in blood. See *Hyperuricemia*.
  excretion, normal and abnormal, *1966*: July, 1032
  kidney disease and, *1966*: July, **1031-1042**

Uric acid *(Continued)*
  kidney disease and, treatment, *1966*: July, 1038
  levels, in gout, *1967*: July, 1037
  metabolism, *1966*: July, 1031
Urinalysis in urinary tract infections, *1966*: July, 1131
Urinary tract, carcinoma, diagnosis, cytologic, *1966*: May, 657
  hemorrhage, antifibrinolytic therapy, *1967*: July, 1068
  infections, etiology, diagnosis and treatment, *1966*: July, **1127-1135**
    gentamicin in, *1967*: Sept., 1146
    hypertension in, *1966*: July, 1011
    nalidixic acid in, *1967*: Sept., 1144
Urine, cultures, in management of infections, *1966*: Sept., 1427
Urobilinogen, fecal and urine, in diagnosis of anemias, *1966*: Nov., 1698
Urography, drip-infusion, in kidney disease, *1966*: July, **957-967**
Uropathy, obstructive, in abdominal aortic aneurysm, *1966*: July, 1023
    renal failure in, *1967*: July, 997
Uterus, bleeding from, postpartum, antifibrinolytic therapy, *1967*: July, 1068
    psychologic aspects, *1967*: Nov., 1376
  carcinoma, diagnosis, cytologic, *1966*: May, 652
    management, *1966*: May, 833-844
    mortality, *1966*: May, 624
  failure of, amenorrhea and, *1968*: March, 347

VACCINATION, encephalitis following, *1967*: May, **701-717**
  precautions, *1967*: May, 585
  routine, of infants and children, *1967*: May, **581-586**
Vaccine(s), adenovirus, *1967*: May, 773
  arbovirus, *1967*: May, **673-679**
  BCG, *1967*: May, **753-764**
    in children, *1967*: May, 583
  cholera, *1967*: May, 630
  common cold, *1967*: May, 767
  influenza, *1967*: May, 783
    in children, *1967*: May, 584
    purified antigens, *1967*: May, 785
    with mineral oil adjuvants, *1967*: May, 785
  measles, *1967*: May, 583, **599-608**
  Mycoplasma pneumoniae, *1967*: May, 798
  poliomyelitis, *1967*: May, **681-692**
    oral, safety of, *1967*: May, 685
  rabies, *1967*: May, **693-700**
  respiratory diseases, acute, *1967*: May, 816

Vaccine(s) *(Continued)*
  rubella, prospects for, *1967*: May, 592
  smallpox, encephalitis following, *1967*: May, 704
    in children, *1967*: May, 584
  typhoid fever, *1967*: May, **617-623**
Vagina, smear test, in amenorrhea, *1968*: March, 348
Vagotomy, insulin test after, *1968*: Nov., 1309
  medical, *1968*: Nov., 1310
Valium. See *Diazepam.*
Valmid. See *Ethinamate.*
Valsalva maneuver as aid to cardiac auscultation, *1966*: Jan., 76
Valves, heart. See under *Heart.*
Vancomycin, for bacterial endocarditis, *1968*: Sept., 1098
  for staphylococcal infections, *1967*: May, 798
    postoperative, *1966*: May, 798
  toxic reactions, *1967*: July, 931
Vanquil, *1967*: Sept., 1204
Varicella, encephalitis following, *1967*: May, 711
    corticosteroids in, *1967*: Sept., 1191
Variola. See *Smallpox.*
Vascular disease, peripheral, neuropathy and, *1968*: July, 905
  symposium on, *1967*: Jan., **1-261**
Vascular surgery, peripheral, use of low molecular weight dextran in, *1967*: Sept., 1293
Vasculitis, allergic, *1966*: March, 406; *1967*: July, 1076, 1081
  in rheumatoid arthritis, *1967*: July, 1024
  nerve biopsy in diagnosis, *1968*: July, 892
Vasodepressor materials from renal medulla, role in hypertension, *1967*: Jan., 9
Vasodilation, in rheumatoid arthritis, factors in, *1968*: May, 629
Vasodilators in hypovolemic shock, *1967*: Jan., 93
Vasomotor center in production of hypertension, *1967*: Jan., 8
Vasopressin therapy, for bleeding esophageal varices, *1968*: Nov., 1465
Vasopressor drugs in shock of myocardial infarction, physiologic basis of use, *1967*: Jan., **69-81**
Vasoxyl. See *Methoxamine.*
Veins, adrenergic receptors in, *1968*: Sept., 1079
  baroreceptor and chemoreceptor reflexes in, *1968*: Sept., 1080
  physical and emotional stimuli and, *1968*: Sept., 1080

Veins (*Continued*)
  reflex stimuli and, *1968*: Sept., 1079
  resistance and capacitance functions of, *1968*: Sept., 1077, 1078
  studies of functioning of, *1968*: Sept., 1078
  tone of, central venous pressure and, *1968*: Sept., **1077-1090**
    in congestive heart failure, *1968*: Sept., 1081
    in hypotension, *1968*: Sept., 1082
    in shock, *1968*: Sept., 1082
    pregnancy and, *1968*: Sept., 1085
  varicose, oral contraceptives and, *1968*: Sept., 1085
    pregnancy and, *1968*: Sept., 1085
Vena cava, superior, occlusion, in lung cancer, treatment, *1967*: March, 568
Venereal disease, epidemiology and prevention, *1967*: May, **735-751**
  rise in, *1967*: May, 735
Venous diseases of legs, phlebography in, *1967*: Jan., **161-174**
Venous pressures, increased, effects of, *1966*: Sept., 1237
Venous pulsations, *1966*: Sept., 1216
Venous thrombosis, fever in, *1966*: Jan., 216
Venous waves, *1966*: Sept., 1216
Ventilation, alveolar, adequate, provision of, in status asthmaticus, *1967*: March, 382, 383
    disturbances, *1967*: March, **403-425**
    methods of calculating, *1967*: March, 422
  assisted and controlled, in status asthmaticus, *1967*: March, 384
  disorders, in heart failure, *1966*: Jan., 39, 44
  support, in acute respiratory failure, *1967*: March, 330
  tests, value, in differentiation of bronchitis and emphysema, *1967*: March, 287
Ventilation-perfusion imbalance in pulmonary embolism, *1967*: Jan., 179
Ventricle, aneurysm of, causes of and surgery for, *1968*: Sept., 1122-1124
  left, dilatation of, surgery for, *1968*: Sept., 1120
    hypertrophy, phonocardiogram in, *1966*: Jan., 100
    outflow obstruction, surgical indications and treatment, *1966*: Jan., **309-323**
  right, overload of, diagnosis, *1966*: Jan., 38, 39, 40
  septal defect in adult, clinical picture, *1966*: Jan., 24
Ventricular fibrillation, primary, after myocardial infarction, *1968*: Sept., 1064
Ventricular premature beats, propanolol for, *1968*: Sept., 1025
Ventricular septum, rupture of, causes of and surgery for, *1968*: Sept., 1124-1126
Veratrum alkaloids in hypertension, *1967*: July, 988
Vertebral artery surgery in stroke, *1967*: Jan., **113-122**
Vesiculobullous eruptions, due to drugs, *1967*: July, 1076, 1080
Vinblastine in Hodgkin's disease, *1966*: May, 827, Nov., 1607
Vinca alkaloids as anticancer agents, *1966*: May, 860, 866
Viomycin in tuberculosis, *1966*: Sept., 1437, 1439
  drug-resistant, in children, *1967*: Sept., 1154, 1162, 1163
Viral agents in gastrointestinal disease, *1967*: May, **637-640**
Viral infections, hematologic disorders due to, *1966*: Nov., 1705, 1708
  respiratory, in military forces, *1967*: May, **769-779**
  vector-borne, immunoprophylaxes, *1967*: May, **673-679**
    impact in Middle Atlantic States, *1967*: May, **661-671**
Viral hepatitis, *1967*: May, **653-660**
Viral pneumonia, in adults, *1967*: May, 793-800, 812
  in children, *1967*: May, 825
Virilism in women, drugs causing, *1967*: July, 897
Viruses, cancer, electron microscopy of, *1966*: May, 889, 894
  oncogenic, *1966*: May, 871
  rheumatoid arthritis and, *1968*: May, 598, 675
Visceral angina, surgical treatment, *1967*: Jan., 219, 224
Vision, disturbed, chromophobe adenoma and, *1968*: July, 827
    chronic renal failure and, *1968*: July, 847
Vitamin B, deficiency of, neuropathy and, *1968*: July, 904
Vitamin B_{12}, absorption, studies of, *1968*: Nov., 1351
    tests, *1966*: Nov., 1694
  deficiency, folic acid deficiency, clinical differentiation, *1966*: Sept., 1249
    recovery from metabolic changes associated with, *1966*: Nov., **1627-1641**
    laboratory diagnosis, *1966*: Nov., 1693, 1694

Vitamin B_{12} (*Continued*)
  deficiency, mechanisms, *1966*: Sept., 1250
  for trigeminal neuralgia, *1968*: July, 797
  for tropical sprue, *1968*: Nov., 1379
Vitamin K malabsorption in gluten enteropathy, *1966*: March, 524
Vitamin K_1 in coagulation defects, *1967*: Sept., 1244
Vitamins, deficiencies, cardiovascular disease and, *1966*: Jan., 303
  water-soluble, absorption, normal, *1968*: Nov., 1344
Vitiligo, in Graves' disease, *1967*: July, 917
Vomiting, in digitalis intoxication, *1966*: March, 502
  in hyperthyroidism, *1966*: March, 585
  in renal failure, *1966*: March, 510
  obstructive, in pyloric obstruction, *1968*: Nov., 1330
Von Bechterew's disease. See *Spondylitis, ankylosing.*

WATER, absorption, normal, *1968*: Nov., 1343
Water, body. See *Fluids, body.*
  imbalance, in renal failure, *1966*: July, 1178
  intoxication, in lung cancer, treatment, *1967*: March, 570
    inappropriate secretion of antidiuretic hormone and, *1968*: July, 817
  metabolism, *1966*: May, 719
Weakness in adrenocortical disease, *1967*: July, 887
Werlhof's disease. See *Purpura, thrombocytopenic, idiopathic.*
Wermer's syndrome. See *Multiple endocrine adenomatosis. 1968*: March, 303
Whiplash injuries, *1968*: July, 775
Whipple's disease, articular manifestations, *1966*: March, 421
  cutaneous melanosis with, *1966*: March, 351
  with arthritis, *1968*: May, 508
Wilson's disease, copper metabolism and, *1968*: July, **989-1001**
  inheritance and gastrointestinal manifestations, *1968*: Nov., 1278
Wolff-Parkinson-White syndrome, phonocardiogram in, *1966*: Jan., 94
Wound, cultures, in management of infections, *1966*: Sept., 1426
  infections, in cancer surgery, treatment, *1966*: May, 791-802
Wrist, in rheumatoid arthritis, surgery of, *1968*: May, 722
Wyamine. See *Mephentermine.*

X-5079C in pulmonary mycoses, *1967*: March, 525
X-rays. See *Roentgen.*
Xylocaine. See *Lidocaine.*

YELLOW fever, immunization, *1967*: May, 673
    encephalitis following, *1967*: May, 708
    for foreign travel, *1967*: May, 843

ZOLLINGER-ELLISON syndrome, *1968*: March, 301
  gastrin and, *1968*: Nov., 1300
  pancreatic manifestations, *1966*: March, 457
  report of a case and clinical appraisal, *1966*: March, **469-478**
Zoster. See *Herpes Zoster.*

~~COPY 2~~

DATE SLIP

MAR 27 1971 B	MAR 29 1971
APR 17 1971	APR 19 1971 B
JUN 19 1971	JUN 18 1971 B
JUL 12 1971	JUL 13 1971
JAN 8 1972	JAN 10 1972 A
MAR 17 1972	MAR 21 1972
NOV 1 1972	NOV 1 1972
NOV 24 1972	NOV 25 1972
FEB 6 1973	FEB 6 1973
FEB 24 1973 N	FEB 23 1973
MAY 14 1975	MAY 9 1975
AUG 27 1975	AUG 27 1975
[illegible] 27 1978	APR 24 1978
MAY 6 1980	APR 30 1980
OCT 29 1980 B	OCT 30 1980
MAY 7 1981 B	MAY 1 1981
AUG 12 1985	

C.U.M.C.
C0114C

CORNELL UNIVERSITY
MEDICAL COLLEGE
1300 York Ave., N.Y.C.

Nov. 19, 1968

MEDICAL LIBRARY

C.U.M.C.
C0114C